A Dissertation on

CORRELATION OF CLINICAL PARAMETERS AND OBJECTIVE ASSESSMENT TOOLS IN ACTIVE THYROID EYE DISEASE

Submitted in partial fulfillment of requirements of

M.S. OPHTHALMOLOGY

BRANCH – III

REGIONAL INSTITUTE OF OPHTHALMOLOGY

MADRAS MEDICAL COLLEGE

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APRIL 2013

CERTIFICATE

This is to certify that this dissertation titled **"CORRELATION OF CLINICAL PARAMETERS AND OBJECTIVE ASSESSMENT TOOLS IN ACTIVE THYROID EYE DISEASE"** is a bonafide record of the research work done by **DR.G.SENTHAMARAI**, post graduate in the Regional Institute of Ophthalmology & Government Ophthalmic Hospital, Madras Medical College and Research Institute, Chennai – 03, in partial fulfillment of the regulations laid down by The Tamil Nadu Dr. M.G.R. Medical University for the award of M.S. Ophthalmology Branch III, under my guidance and supervision during the academic years 2010 – 2013.

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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"CORRELATION OF CLINICALPARAMETERS AND OBJECTIVE ASSESSMENT TOOLS IN ACTIVE THYROID EYE DISEASE"** is a bonafide and genuine research work carried out by me under the guidance of **Prof. Dr. M. Subhashini, M.S., D.O.,**

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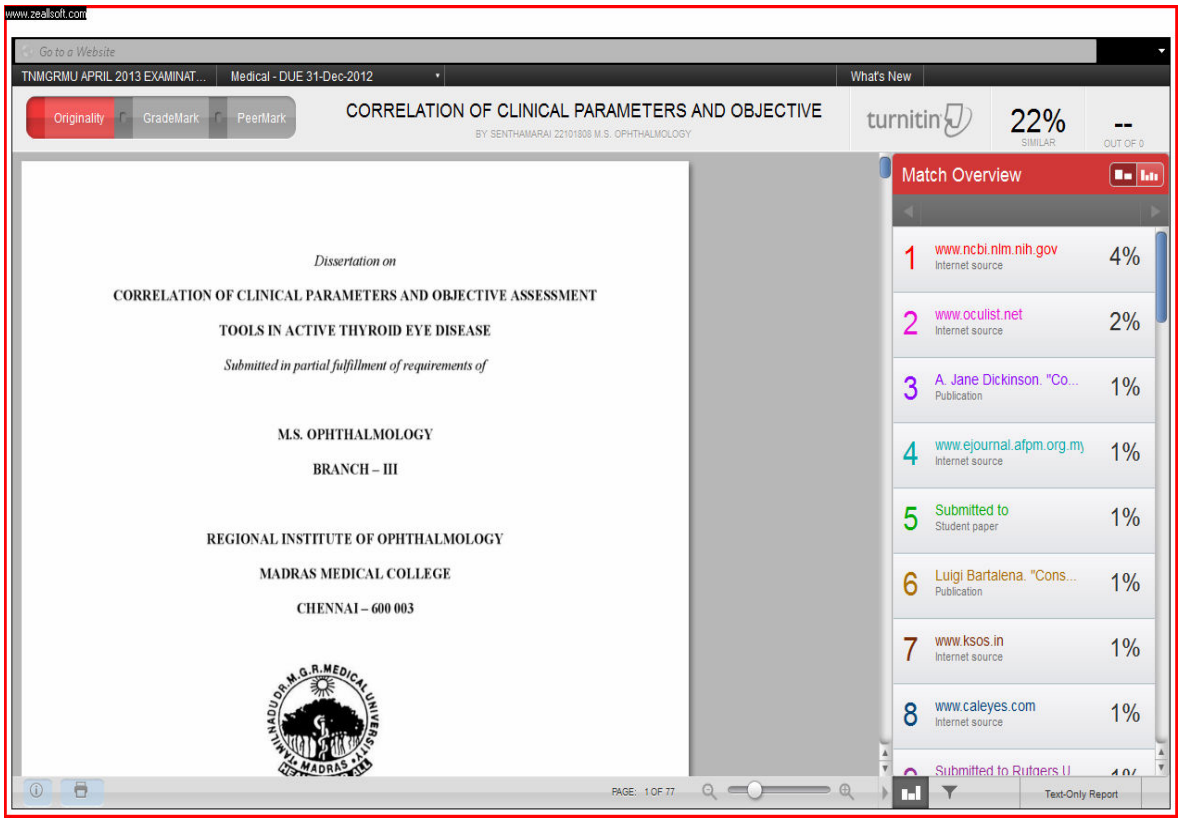
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CONTENTS

S.NO	TITLE	PAGE NO.
	PART I	
1.	INTRODUCTION	1
2.	HISTORY	2
3.	PHYSIOLOGY OF THYROID HORMONE	3
4.	ANATOMY OF ORBIT	6
5.	PATHOGENESIS	11
6.	IMMUNOLOGY OF THYROID EYE DISEASE	14
7.	CLASSIFICATION	15
8.	CLINICAL MANIFESTATION	18
9.	EVALUATION	23
10.	MEDICAL MANAGEMENT	26
11.	SURGICAL MANAGEMENT	30
	PART II	
13.	AIMS AND OBJECTIVES	35
14.	INCLUSION CRITERIA	36
15.	MATERIALS AND METHODS	37
16.	OBSERVATION AND DISCUSSION	41
17.	RESULTS	71
18.	CONCLUSION	75
	PART III	
19.	REFERENCES	76
20.	PROFORMA	82
21.	KEY TO MASTER CHART	86
22.	MASTER CHART	87

ABBREVIATION

TED- Thyroid Eye disease

TPO- Thyroid peroxidase

MIT - Mono iodo tyrosine

DIT- Di Iodo Tyrosine

TBG- Thyroid Binding Globulin

IGF- 1-Insulin Like Growth Factor-1

TSHR-Thyroid Stimulating Hormone Receptor

GAG- Glycosaminoglycans

IOP- Intraocular Pressure

SR- LPS-Superior Rectus-Levator Palpebrae Superioris complex

IR- Inferior Rectus

MR- Medial Rectus

SO- Superior Oblique

EOM-Extraocular Muscles

VA- Visual Acuity

CAS- Clinical Activity score

IV MP- Intravenous Methyl Prednisolone

BSV- Binocular single vision

PART - I

INTRODUCTION

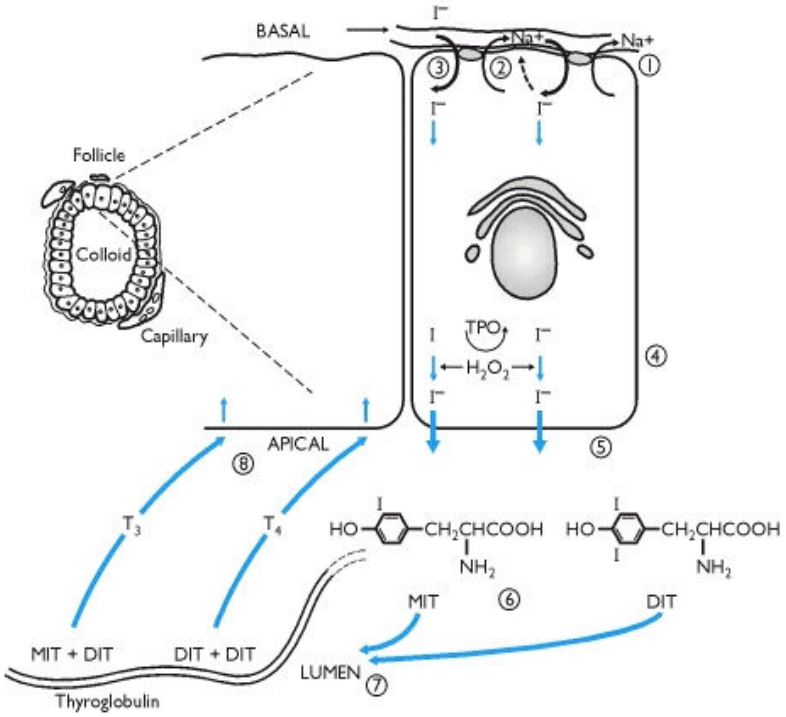
Thyroid eye disease (TED) also known as Graves Orbitopathy, is typically self-limiting autoimmune process associated with dysthyroid status. Incidence of TED is 90% in graves disease,3% in Hashimoto's Thyroiditis,1% in primary Hypothyroidism, and 6% in Euthyroid status and at least 50% of these patients develop clinically evident symptomatic TED. The patients may present as mild disease to severe irreversible disease. In 5-10% of patients vision loss occurs due to corneal decompensation or optic nerve compression.TED affects women 2.5-6 times more frequently than men, in older age female : male ratio decreases. The peak incidence is in second to fifth decade, severity increases with older than 50 years. Smoking is strongly associated with TED due to generalized stimulation of autoimmune disease and effect of hypoxia on orbital fibroblast. Diabetics tends to have more severity in TED.

HISTORY

Thyroid-related orbitopathy has been recognized by the medical community since 200 years. Caleb Parry showed the association between eyeball enlargement and goiter in the year 1786 .In 1835, Robert J Graves described the symptom complex of thyroid enlargement, protrusion of eyes and palpitation. Adolph von Basedow also described these features in the same period

PHYSIOLOGY OF THYROID HORMONE

Secretion of thyroid hormones Approximately 100 μg of thyroid hormones is secreted each day, mostly in the form of T4 with about 10% as T3. Eighty percent of the T4 undergoes peripheral conversion to the more active T3 in the liver and kidney (T3 is ten times more active than T4) or to reverse T3 (rT3) that has little or no biological activity. Excess iodine given to a person with normal thyroid gland activity leads to an initial reduction in organification and hormone synthesis and secretion, ***the Wolff-Chaikoff effect***. 'Escape' from this inhibition, generally occurs after several days.



Uptake and organification of iodine by the thyroid gland

1. Active iodide uptake. (I-) in exchange for Na+.
2. Iodide discharged from the follicular cell by competing ions such as perchlorate, bromide or chlorate.
3. Iodide uptake is stimulated by TSH (the main control point for hormone synthesis).
4. TPO causes Oxidation of iodide by hydrogen peroxide (H2O2) to form active iodine.
5. Active transport of iodine across the apical surface of the follicular cell.
6. Formation of mono- and diiodotyrosines (MIT and DIT) by incorporation of active iodine into thyroglobulin molecule.
7. Uptake of the thyroglobulin into the lumen of the follicle
8. About 1% of stored colloid is removed each day. When the gland is very active this may rise to nearly100% and colloid stores are depleted.

THYROID HORMONE TRANSPORT:

Over 99% circulating thyroid hormones are bound to plasma proteins of which about 70% is bound to TBG, 10–15% to transthyretin

and 20-15% to albumin. Only a tiny fraction is in the 'free' form. Comparison of the serum concentrations of T4 and T3

T4 T3

Serum concentration	T3	T4
Total	100nmol/l	2nmol/l
Free	20pmol/l	5pmol/l

Serum half lives: T4 — 7 days, • T3 — 1 day, rT3 — 4 hours.

FUNCTIONS OF THYROID HORMONE:

Every cell in the body is acted upon by thyronine. increase in basal metabolic rate, regulation of long bone growth in synergy with growth hormone and neuronal maturation, affects protein synthesis, increase the body's sensitive response to catecholamines by permissiveness. Hormones regulate protein, carbohydrate and fat metabolism. Thyroid hormones helps in heat generation.

ANATOMY OF ORBIT

The complex of neurosensory, vascular, motor, and secretory structures within the orbit are confined to 30 cm^3, bounded anteriorly by the lids, and surrounded by bone, nasal sinuses, intracranial contents, and deep facial structures. The orbit is pyramidal in shape with an overall volume of 30 cm^3, of which the eye constitutes 7 cm^3.

DIMENSIONS:

Height of orbital opening - 35mm

Width of orbital opening - 40mm

Depth of orbit - 40mm

Interorbital distance - 25mm

The Orbital walls are composed seven bones:

Ethmoid, frontal, lacrimal, maxillary, palantine, sphenoid and zygomatic.

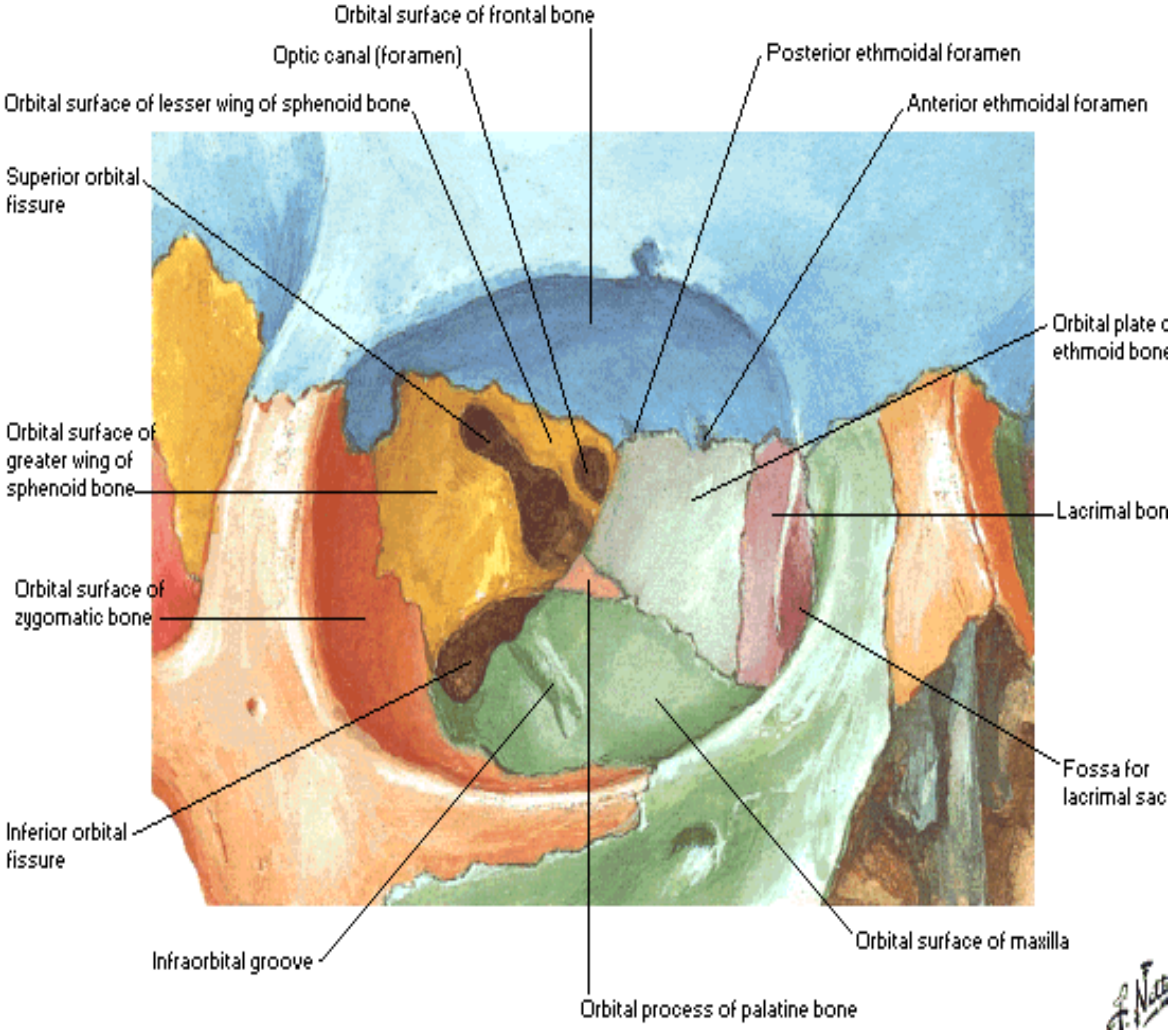
THE ORBITAL ROOF:

It is triangular in shape Formed by lesser wing of the sphenoid and the orbital part of frontal bones, which may have within it a posterior extension of the frontal sinus. Apically, the lesser wing contains the optic canal, which is 5 mm to 6 mm in diameter, 10 mm to 12 mm in length and

has an axis of 36 to the sagittal plane. Thus, the optic canals are separated anteriorly by 3 cm and posteriorly by 2.5 cm.

THE LATERAL WALL:

It is made up of the greater wing of the sphenoid, frontal, and zygomatic bones, and is at an angle of 45 to the medial wall. It is 4.5 cm to 5.0 cm long, and is the strongest orbital wall. Posteriorly, it is separated from the roof by the superior orbital fissure and from the floor by the inferior orbital fissure. Laterally, it forms a portion of the temporalis fossa and is thinnest at the suture line between the greater wing of the sphenoid and the zygomatic bone (where it can be fractured easily at surgery). Posteriorly, the inferior orbital fissure communicates with the pterygopalatine and infratemporal fossa.


Orbital surface of frontal bone
Optic canal (foramen)
Posterior ethmoidal foramen
Orbital surface of lesser wing of sphenoid bone
Anterior ethmoidal foramen
Superior orbital fissure
Orbital plate o ethmoid bone
Orbital surface of greater wing of sphenoid bone
Lacrimal bon
Orbital surface of zygomatic bone
Fossa for lacrimal sac
Inferior orbital fissure
Orbital surface of maxilla
Infraorbital groove
Orbital process of palatine bone

THE MEDIAL WALL:

It is the thinnest (0.2 mm to 0.4 mm) and is made up of the maxillary, lacrimal, ethmoid, and lesser wing of sphenoid. About 24 mm from the anterior lacrimal crest is the anterior ethmoid foramen, and 12 mm behind this is the posterior ethmoid foramen, which is approximately 6 mm from the optic canal (described by the mnemonic, "24-12-6"). These foramina mark the horizontal level of the cribriform plate at the fronto ethmoid suture line. The ethmoid and frequently the sphenoid and maxillary sinuses form part of the medial wall.

THE FLOOR:

It is shorter, triangular, and is made up of the maxillary, zygomatic, and palatine bones. The infraorbital sulcus originates about 2.5 cm to 3 cm from the inferior orbital rim and forms the infraorbital canal halfway along its course, which opens on the maxilla at the infraorbital foramen. The maxillary and often some of the ethmoid sinuses are immediately adjacent to the floor. The thinnest point is medial to the infraorbital sulcus and canal, where it can be fractured easily at the time of decompression surgery.

CONTENTS OF ORBIT:

Eyeball occupying 1/5th of volume, extraocular muscles, LPS and mullers muscle of Orbit. Orbital nerves-3, 4, 6th cranial nerve, branches of ophthalmic division of fifth nerve and branches of maxillary division of 5TH nerve(infraorbital and zygomatic nerve).Vessels-ophthalmic artery and its branches,infraorbital vessels,orbital branch of middle meningeal artery,and superior and inferior ophthalmic vein. Orbital fat, reticular tissue and orbital fascia,lacrimal gland and lacrimal sac.

PATHOGENESIS

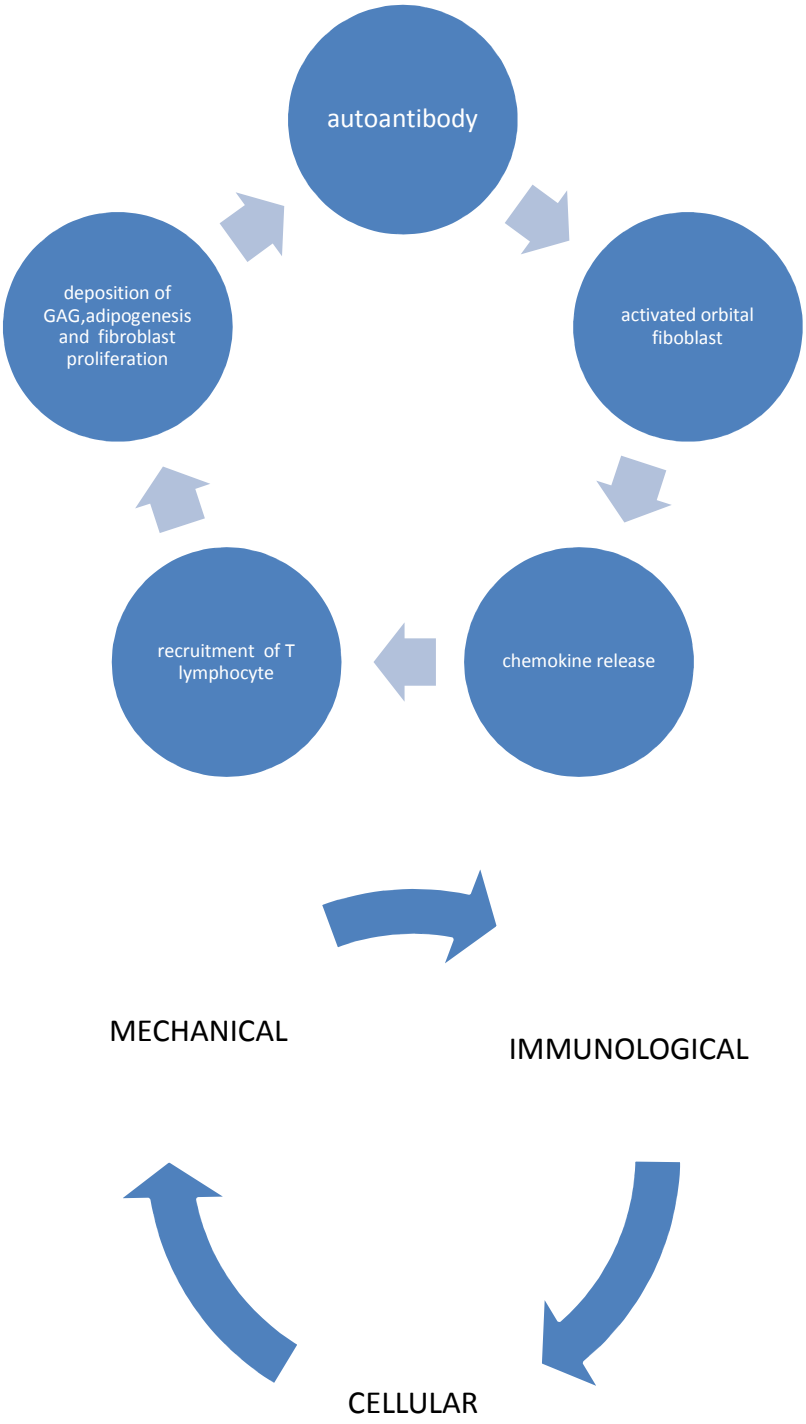
AUTOIMMUNITY:

More than 45 theories has been proposed but still the pathogenesis remains unclear. Interaction between obital fibroblast ,cytokines, immune cells, auto antibody, environmental and genetic factors resulted in increase in size of extraocular muscles and orbital fat because the orbital tissue and thyroid share a common antigen. Thyrotropin receptors (thyroid-stimulating hormone receptor – TSHR) may play a role as an autoantigen in Graves' hyperthyroidism, orbitopathy, and pretibial myxedema. Antigens may be thyroglobulin, TSH receptor,IGF-1 receptor, or extraocular muscle antigen.

SMOKING:

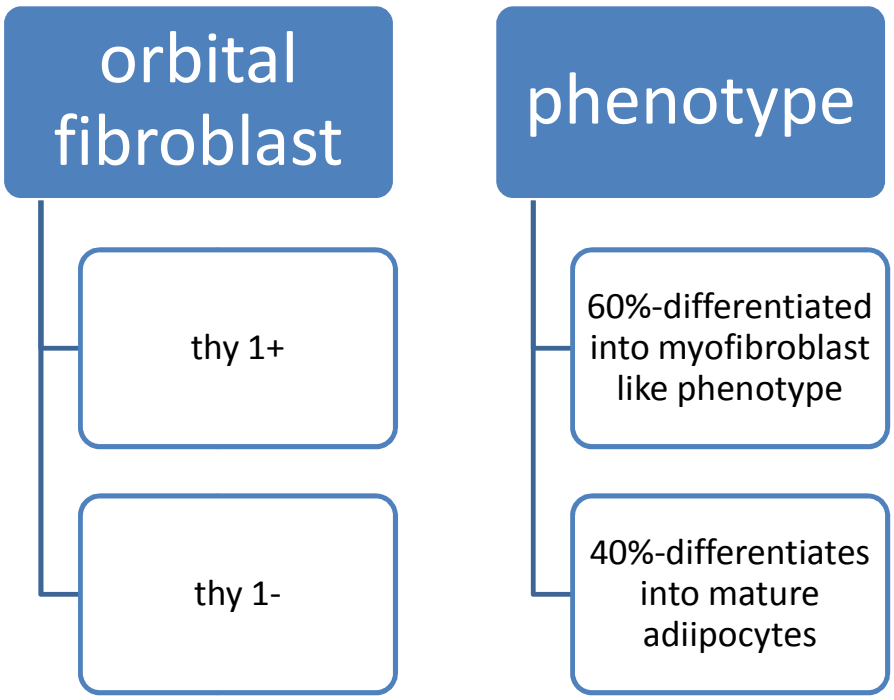
Smoking increases the incidence and severity of TED, 5times higher risk than those who do not smoke. Dose dependent statistically increase in GAG production and adipogenesis. Genetic Predisposition20-60% of affected individuals have positive family history of thyroid eye disease. A population based study of Danish monozygotic twins showed 30% concordance rate. HLA- B8, DR3, andDQA1*0501 haplotypes increases susceptibility to the disease and HLA-DR B1*07 offers protection.

LEHMAN AND COLLEAGUES (PLAUSIBLE PATHWAY)



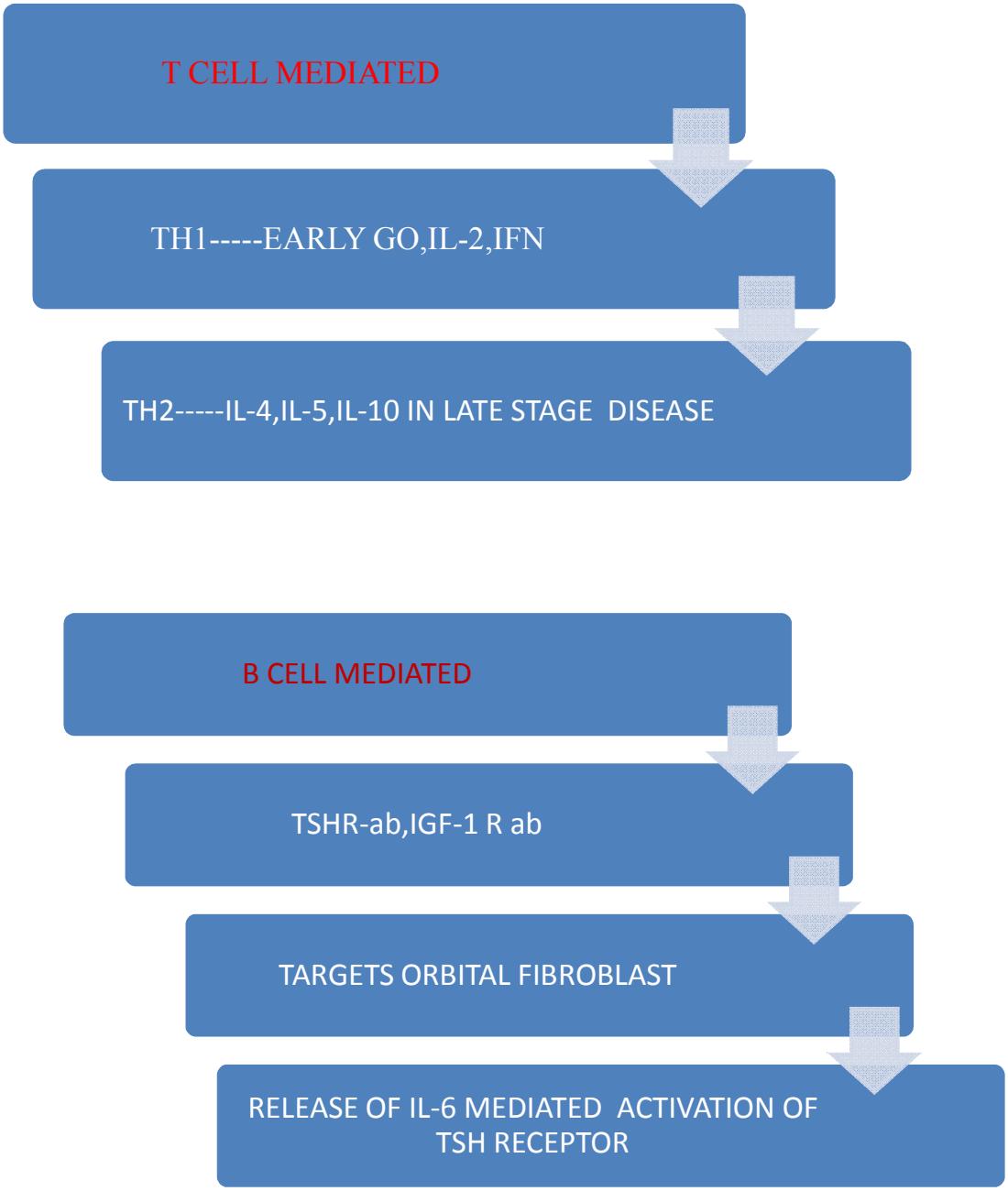
ORBITAL FIBROBLAST:

It is derived from neural ectoderm whereas other fibroblasts are derived from mesenchyme. Orbital fibroblast has unique phenotype, that can differentiate into adipocytes and myofibroblasts.



IMMUNOLOGY OF THROID EYE DISEASE

Both T cell mediated and B cell mediated



CLASSIFICATION

Werner Classification

Class	Grade	Mnemonic	Suggestions for Grading
0		N	No physical signs or symptoms
1		O	Signs only
2		S	Soft tissue involvement
	0		Absent
	A		Minimal
	B		Moderate
	C		Marked
3		P	Proptosis of 3 mm or more
	0		Absent
	A		3–4 mm
	B		5–7 mm
	C		8 mm or more
4		E	Extraocular muscle involvement
	0		Absent
	A		Limitation of motion at extremes of gaze
	B		Evident restriction of motion
	C		Fixation of globe
5		C	Corneal involvement
	0		Absent
	A		Punctate lesions
	B		Ulceration
	C		Necrosis or perforation
6		S	Sight loss (due to optic nerve)
	0		Absent
	A		20/20–20/60 (<6/6 – 6/18)
	B		20/70–20/200 (<6/18 – 6/60)
	C		Worse than 20/200 (<6/60)

Simplest classification-TYPEI AND TYPE II NON INFILTRATIVE OR TYPEI-minimal inflammation and minimal restrictive myopathy. INFILTRATIVE OR TYPE II-Significant orbital inflammation and restrictive myopathy.

RISK FACTORS:

Male gender, older age, degree of initial thyroid imbalance, smoking, Diabetes, acute onset of the disease,

BASED ON THE ACTIVITY OF DISEASE:

MILD	MODERATE	SEVERE
Adolescent, young adult onset Lid lag Lid retraction Lagophthalmos Proptosis	Permanent lid retraction Lid lag Proptosis Soft tissue changes Intermittent myopathy	More rapid onset Most freq in old age group. Predominant inflammatory cicatricial,mass effect
Regress with control of hyperthyroidism	Usually settles within 6months-1yr Imaging-Disproportionate proptosis with mild EOM enlargement, Increase in fat content	Progressive exophthalmos Soft tissue involvement, Progressive myopathy Optic neuropathy

ITEDS-INTERNATIONAL THYROID EYE DISEASE GROUP-has developed VISA-VISION, INFLAMMATION, STRABISMUS, APPEARANCE CLASSIFICATION devised by DOLMAN AND ROOTMAN based on international working group suggestion. This helps direct appropriate management for patients with TED in a logical sequence.

CLINICAL MANIFESTATIONS

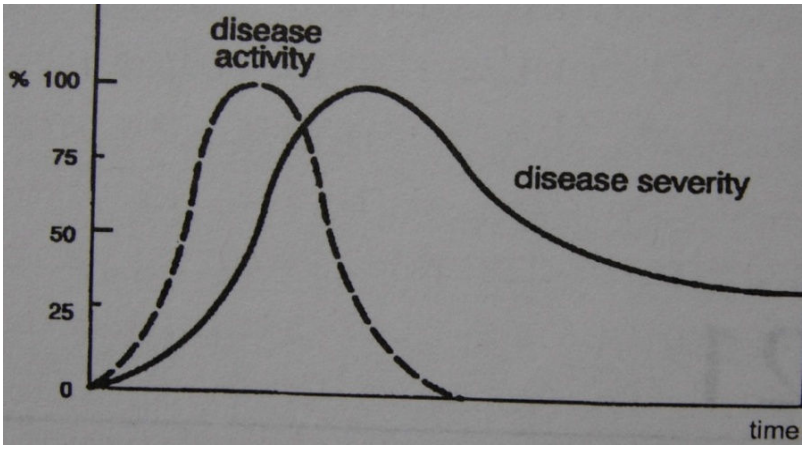
The clinical manifestations of thyroid orbitopathy are mainly due to edema inflammation, and fibrotic changes within the soft tissues of the orbit.

NATURAL HISTORY:

During the course of TED, the disease passes through several phases.

1. Dynamic phase of progressive deterioration
2. Plataeu phase
3. Improvement
4. Static/burnt out phase

RUNDLES CURVE



Presentation:

Lid retraction	–	35 - 60 %
Lid lag	–	40 - 50 %
Increased IOP	–	30 %
Proptosis	–	30 %
Extreme proptosis	–	3 - 7%
Malignant exophthalmos	–	2- 7 %

LID RETRACTION:

Most common cause for upper lid retraction is TRO. It may be due to Sympathetic overactivity, Fibrosis & contracture of levator / SR complex, Tethering of IR causing accentuation of lid retraction in upgaze. Greater amount of sclera visible temporally than nasally called temporal flare due to fibrosis of lacrimal gland fascia and leavator aponeurosis. Lower lid retraction is due to fibrosis of capsulopalpebral fascia.

DIFFERENTIAL DIAGNOSIS:

Neurological disease, Marcus gunn phenomenon,Midbrain disease like Hydrocephalus, Parinauds syndrome, Trauma/aneurysm involving 3rd nerve, Sympathomimetic drugs, Cirrhosis, Congenital, Post surgical causes like ptosis, Post traumatic and idiopathic .

RESTRICTIVE MYOPATHY:

EOM Involvement in 30 – 50 % of patients with TRO, tendons will be spared. Initially due to inflammation and later fibrosis there may be associated restriction of elevation due to IR fibrosis. Diplopia in upgaze is the common complaint in these patients. IR > MR > SR-LPS > LR. May also mimic superior oblique palsy

IOP IN THYROID ORBITOPATHY:

May be raised in 30 % cases in patients with restrictive myopathy.IOP may increase by 4mm Hg in upgaze, IOP >9mm of Hg correlates with optic neuropathy. Elevated episcleral venous pressure due to obstruction of orbital veins can cause elevation of IOP.

DIFFERENTIAL DIAGNOSIS:

Idiopathic myositis, pseudotumour, Sarcoid, Wegener's granulomatosis, metastasis to EOM, Carotid-cavernous fistula, Amyloid, Collagen vascular diseases.

SOFT TISSUE SIGNS:

Lid edema and erythema, conjunctival chemosis and caruncular edema

EXOPHTHALMOS:

TED is the most common cause of both unilateral and bilateral axial proptosis in adults. Measurement of 2 mm or more above normal limit (20mm) is absolute, relative when compared with other eye and the basal reading is kept constant to follow up the patient for comparative study. When the pressure within the retrobulbar tissues exceeds the forces counteracting proptosis, the rare complication of subluxation of the globe anterior to the eyelid may occur. The increased orbital volume is usually due to both extraocular muscle and orbital fat expansion, younger patients exhibit more of fat involvement and older patients more of muscle.

EXOPHTHALMOMETRY:

Mild	:	21-23mm
Moderate	:	24-27mm
Marked	:	28mm or more

EXPOSURE KERATITIS:

It can occur due to Proptosis, inadequate Bell's phenomenon and Superior limbic keratoconjunctivitis can coexist.

OPTIC NEUROPATHY:

Incidence < 5 %, but most common cause of blindness. More common in males, usually older patients. Compression of optic nerve at orbital apex by enlarged extraocular muscle and inflammation of optic nerve sheath. It can occur without significant proptosis. 18 % of patients may have VA 6/6 to 6/9, abnormal disc (swollen / pale) in 52 %, Visual field defects in 66% and Colour Vision may not be reliable (esp. Ishihara).

EVALUATION

Evaluation of patients presenting initially or referred from endocrinology department as a known case of hypo/hyperthyroidism, detailed history taking with regard to disease onset, duration and rate of progression of the disease, history of smoking and history pertaining to ocular symptoms like pain, redness, foreign body sensation, photophobia, defective vision, double vision were noted. Complete ophthalmology workup included Visual acuity, slit lamp examination of anterior segment, pupillary reaction, extraocular movements, differential intraocular pressure measurement, Hertels Exophthalmometry, schimers test ,fields, colour vision, diplopia charting, fundus examination, forced duction test.

SEROLOGICAL TEST:

Serum level-IL6, HS-CRP, RBS, Free T3, T4, TSH (stimulation of IGFR-1R with IGF-1 or immunoglobulin G shown to increase IL 6, fibroblast causes increased expression of TSHR which resulted in upregulation of TNF-α and IL-6.)

IMAGING:

CT SCAN ORBIT-axial and coronal view-more sensitive than MRI in identifying extraocular muscle enlargement. CT Findings: Tendon sparing muscle belly enlargement, apparent increase in orbital fat volume, and apical crowding of optic nerve.

B SCAN (*Orbital ultrasound OTI Scan -1000 with ultrasound probe of 7.5-10 MHZ)* provides topographic information of extraocular muscles Medium gain setting with patient fixating towards the muscle being examined, longitudinal mode with probe placed opposite to muscle. Internal structure & reflectivity evaluated in anterior $1/3^{rd}$ -1/2 of muscle.Double peaked sheath spikes indicates that perpendicularity is achieved. The findings are -Tendon sparing extraocular muscle enlargement, Heterogenous irregular echoes, swelling of orbital fat and lid tissues, Enlargement of lacrimal gland and Optic nervehead thickening. A scan -moderate to low intense spikes due to large interfaces with in the muscle due to edema and inflammatory cells. Bilateral asymmetrical muscle thickening is key for diagnosis

Extraocularmuscle Thickness (normative data) Byrne et al

MR	2.3-4.7mm
IR	1.6-3.6mm
LR	2.2-3.8mm
SR/LPS	3.9-6.8mm
SUM OF ALL MUSCLES	11.9-16.9mm

MEDICAL MANAGEMENT

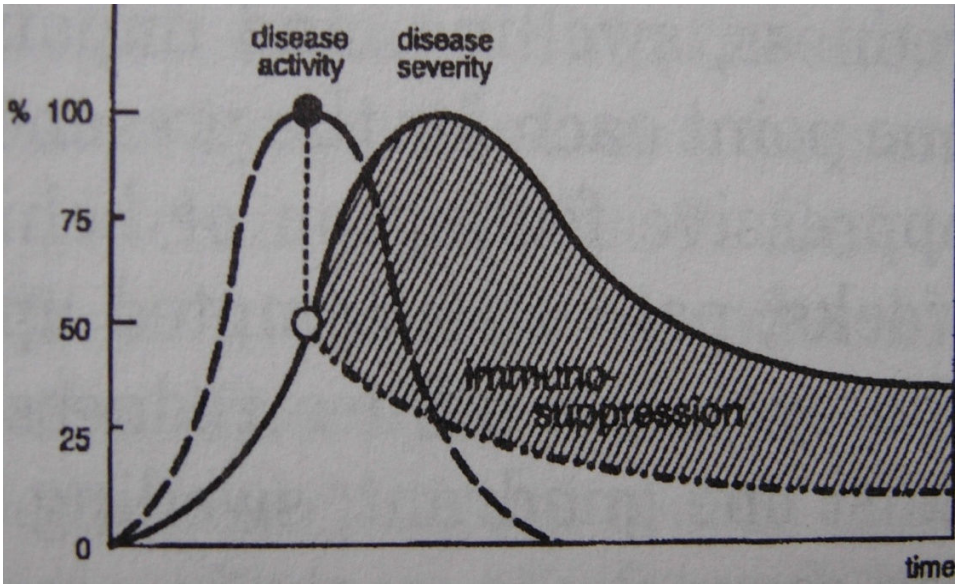
Step wise evaluation

Step 1 is to Re-establish euthyroidism

Step 2 is to stop smoking and conservative managment.

Step 3 is to determine the activity and severity of disease

Step 4 is to assess the severity which determines the treatment regime.



`Active' disease implies the presence of inflammatory features and suggests the potential to respond to anti-inflammatory treatments. `Inactive' disease defines no inflammation, yet residual fibrosis and secondary effects may persist. In inactive phase only surgical treatment can alter the outcome. Severity describes the degree of functional or cosmetic deficit at any stage. It is important to determine the phase for

formulating an appropriate management because immunomodulatory therapy can only be effective while there is active inflammation.

Categorizing the patients as clinically active if CAS SCORE is 4 or more and severe ophthalmology based on the parameters like degree of proptosis, diplopia, compressive optic neuropathy and corneal involvement. Patients in active stage is again categorized into mild, moderate and severe disease.

MILD DISEASE:

Patients are advised to get endocrinologist opinion for control of Thyroid Status, advised to stop smoking, topical lubricating eye drops and head end elevation of bed. Kept under observation.

MODERATE DISEASE:

Patients are categorized into active or inactive stage. Those in active stage were treated with oral steroids and if not responding low dose radiotherapy is given. Patients in inactive stage can be taken up for rehabilitative surgery like orbital decompression, strabismus surgery followed by lid surgery.

SEVERE DISEASE

Patients in severe disease were treated with IV Steroids, Orbital radiation with or without steroids, Orbital decompression in case of compressive optic neuropathy

PROVEN THERAPIES

Corticosteroids

Acts as anti-inflammatory and immunosuppressive agent, and reduces synthesis and secretion of glycosaminoglycons. Oral/Local/ Intravenous administration**.** Proptosis will less likely to respond and not good for long term therapy**.** Complications include Hypertension, Diabetes mellitus, Cataract, glaucoma, infection, peptic ulcer and Osteoporosis.

CONTROL OF SEVERITY

Pulse therapy with ***IV Methylprednisolone*** 1 gm daily for 3days at 6 weekly interval. Response to treatment is monitored for 4-6weeks and cycles can be repeated upto 4times.IVMP will cause lymphocytolysis when compared to oral steroids which causes suppression of inflammation. Retro-bulbar Triamcinolone in the dose of 40mgs/week per orbit for 4 weeks can be given.

ORBITAL RADIATION

Typical dosage is 20 Gy in 10 Fractions (2 Gy /trt.), ***lower dose is (10 Gy***) that is 1 Gy per week for 20 weeks. It should be avoided in mild stable disease, in young patients and less effective for proptosis. But improves soft tissue signs, compressive optic neuropathy and extraocular motility disorders.

Immunosuppressants (*steroid sparing agent)*

Oral Methoterxate: dosage is 7.5mgs/week for 2 weeks**,**10mgs/week for 2 weeks and 12.5mgs/week for 5 months, Cyclosporine 7.5 mgs/kg/day, Azathioprine, cyclophosphamide**,** Ciamexon which inhibits expression of HLA DR antigen, are other immunosuppessants.

OTHER THERAPIES

Plasmapheresis, Somatostatin analogues like Octreotid 0.1 mg SC tds / 3 months, Lantreotide 40 mgs every other week for 3 Months, IV immunoglobulins, Anti-oxidants like Selenium 200 mcg/day Rituximab (RTX)-Anti-CD20 monoclonal antibody,can cause peripheral B-cell depletion and Pentoxyphyline.

SURGICAL MANAGEMENT

ORBITAL DECOMPRESSION

INDICATIONS are failed medical therapy, Progressive compressive optic neuropathy and exposure keratopathy, Globe subluxation, Pain from tight orbit, Imaging showing evidence of enlarged muscles and cosmetic purpose.

HISTORY

1911 – Dollinger – modification of Kronlein lateral orbitotomy

1931 – Naffziger – Transfrontal approach

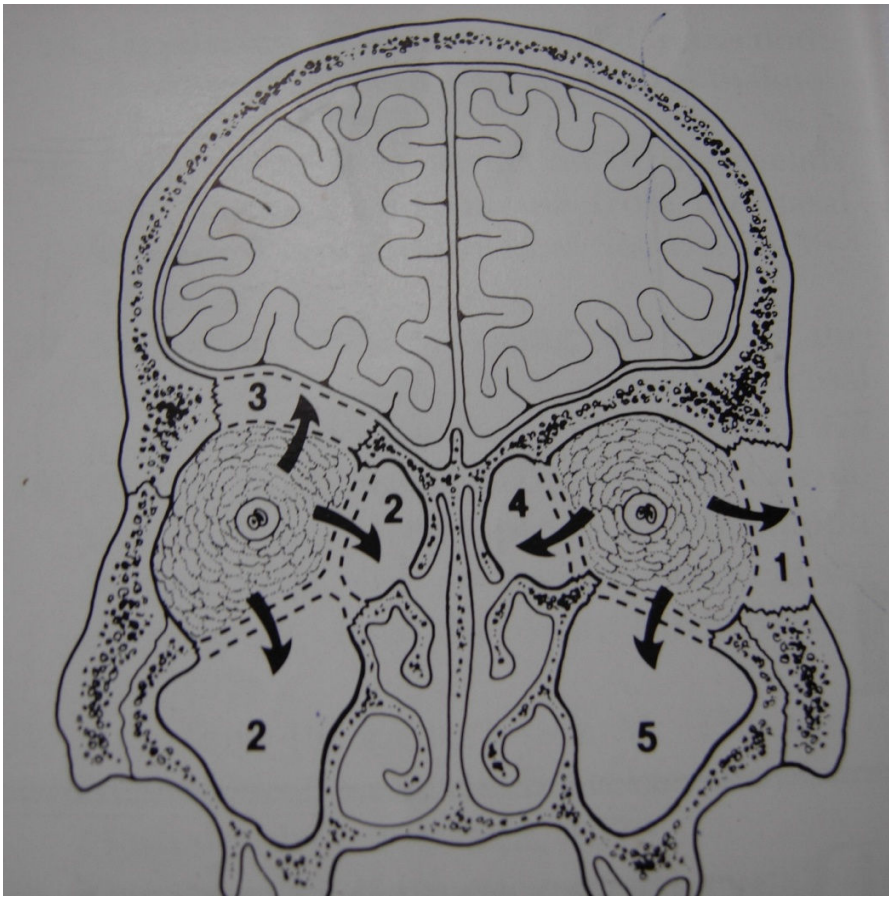
1936 – Sewall's – Ethmoidectomy

1950 – Hirsch & Urbarek – inferior orbitotomy

1957 – Walsh & Ogura – medial & inferior orbitotomy

1990 – Kennedy – endoscopic decompression

Olivari – removal of orbital fat



Techniques described are one-two-three and four wall orbital decompression. The floor and medial wall are most commonly decompressed. The concept of balanced decompression involves removal of lateral and medial wall with sparing the floor with the aim of limiting inferomedial globe displacement and consequent motility disturbance and diplopia.

LATERAL ORBITAL DECOMPRESSION

First wall to decompress.Secondary strabismus is minimal and 2-4mm of Globe retroplacement but minimally effective in decompression of optic nerve.

MEDIAL WALL DECOMPRESSION

Effective in decompression of optic nerve with globe retroplacement of 5.5 mm, modified by Ogura. Diplopia is common following the procedure**.**

TRANSFRONTAL DECOMPRESSION

Neurosurgical approach and effective in B/L optic nerve decompression. Frontal lobe signs, pulsating globe, probable meningitis can occur. Globe retroplacement upto 3mm.

BONE REMOVAL ORBITAL DECOMPRESSION (BROD)

Indication for BROD is small bony orbital volume with Small orbital fat or enlarged muscles with Compressive optic neuropathy.

FAT REMOVAL ORBITAL DECOMPRESSION (FROD*)*

Indication includes large bony volume with large orbital fat volume with stretched muscles and for cosmetic purpose. 6cc of fat removal causes decrease in proptosis by 4.7mm.

STRABISMUS SURGERY:

Diplopia is one of the most functionally disabling aspect of thyroid eye disease due to asymmetric restriction of the extraocular muscles. The goal of strabismus surgery is to achieve BSV in primary and down gaze. The most frequently performed procedure is MR or IR recession. Use of adjustable suture to prevent over or under correction. The inferior and medial rectus muscles can be recessed safely up to 6–7 mm. Marginal myotomies can also help to weaken the restricted muscle. The number of operated rectus muscles to no more than three per eye to avoid anterior segment ischemia.

EYELID SURGERY:

Measurement of eyelid retraction should be stable for up to 6 months and should follow the squint surgery. In the upper lid, total levator muscle recession and partial mullers muscle resection can be done along with anchoring the recessed levator muscle is secured with hang back sutures anchoring to the conjunctiva, or using scleral graft between the recessed muscle and tarsal plate.

PART - II

AIMS AND OBJECTIVES

To analyze the correlation of clinical parameters and significance of objective assessment tools in active Thyroid Eye Disease.

Primary objective: Clinical assessment of Thyroid Eye Disease, to identify disease in active phase and start medical management, thereby reducing the disease severity.

Secondary objective: To analyze whether the objective tools support in aiding the diagnosis of activity in Thyroid Eye Disease.

INCLUSION CRITERIA

Clinically diagnosed cases of TED with following features:

Lid signs

Soft tissue changes

Restrictive myopathy

Bilateral axial proptosis were included in our study.

Patients in chronic stable phase were excluded from study.

MATERIALS AND METHODS

Prospective observational study, conducted at Regional Institute of Ophthalmology, Egmore, Chennai from June 2010 till June 2012.Sample size was thirty patients in the age group of 20 to 60yrs.

METHODS

Evaluation of patients presenting initially or referred from endocrinology department as a known case of hypo/hyperthyroidism, detailed history taking with regard to disease onset,duration and rate of progression of the disease, history of smoking and history pertaining to ocular symptoms like pain, redness, foreignbody sensation, photophobia, defective vision, double vision were noted.

Complete ophthalmology workup included

Visual acuity, lid signs, slit lamp examination of anterior segment, pupillary reaction, extraocular movements, fundus examination, fields, colour vision, diplopia charting, schimers test, Hertels Exophthalmometry, differential intraocular pressure measurement and forced duction test were done.

Blood examination: Serum level-IL6, HS-CRP, RBS, serological test-FreeT3, T4, TSH. Categorizing the patients as clinically active if CAS SCORE is 4 or more and severe ophthalmology based on the parameters like proptosis, diplopia and optic neuropathy.

Objective disease assessment tools includes

B scan OTI 1000 wit7.5-10 MHz was used in our study that provides topographic information of extraocular muscles using medium gain setting with patient fixating in primary gaze and Longitudinal mode with probe placed opposite to the muscle being examined. Internal structure and reflectivity was evaluated in anterior $1/3^{rd}$ -1/2 0f muscle. Double peaked sheath spikes indicates that perpendicularity is achieved .Tendon sparing muscle enlargement with corresponding low reflectivity is observed in A scan.

CT SCAN ORBIT-AXIAL AND CORONAL VIEW

All patients underwent CT orbit for the evidence of Tendon sparing extraocular muscle enlargement with apical crowding or fat hypertrophy was observed.

BIOCHEMICAL PARAMETERS:

IL-6, HS-CRP, TFT was done and their correlation with activity of TED was analysed. The serum samples of patients in moderate and active stage are taken and IL-6 and HS-CRP using ELISA was done. The results were compared with patients in control group without TED.

The patients diagnosed clinically as TED were categorized as mild, moderate and severe activity. Endocrinologist opinion was obtained for all patients and treatment of systemic thyroid dysfunction was started. Thyroid status was kept under control and advised to stop smoking.

Patients in mild stage were given supportive management like topical lubricant eye drops, head end elevation .Patients are followed up every 6 months and monitored clinically for disease progression.

Patients in moderately active stage were treated with oral Prednisolone 1mg/kg body weight given for 4-6weeks and followed up every 2 weeks to assess the disease activity, visual acuity, pupil for RAPD, extraocular movements and Hertels exophthalmometry were performed. If patients are symptomatically better with resolving signs of activity the steroids are continued in the same dosage for 2 weeks and then tapering is done.

Patients in severe active stage based on subjective ocular symptoms and clinical features like soft tissue signs with extraocular movement restriction with diplopia, severe proptosis and compressive optic neuropathy. Radiological evidence showing apical crowding and A scan showing low eye muscle reflectivity were started with IV pulse therapy with Methyl prednisolone 1gm diluted in 500ml normal saline infused over 30 minutes for three days and patients are discharged with oral steroids(40-60mg).Patients are reviewed every week for signs of activity, optic nerve compression and steroid side effects .

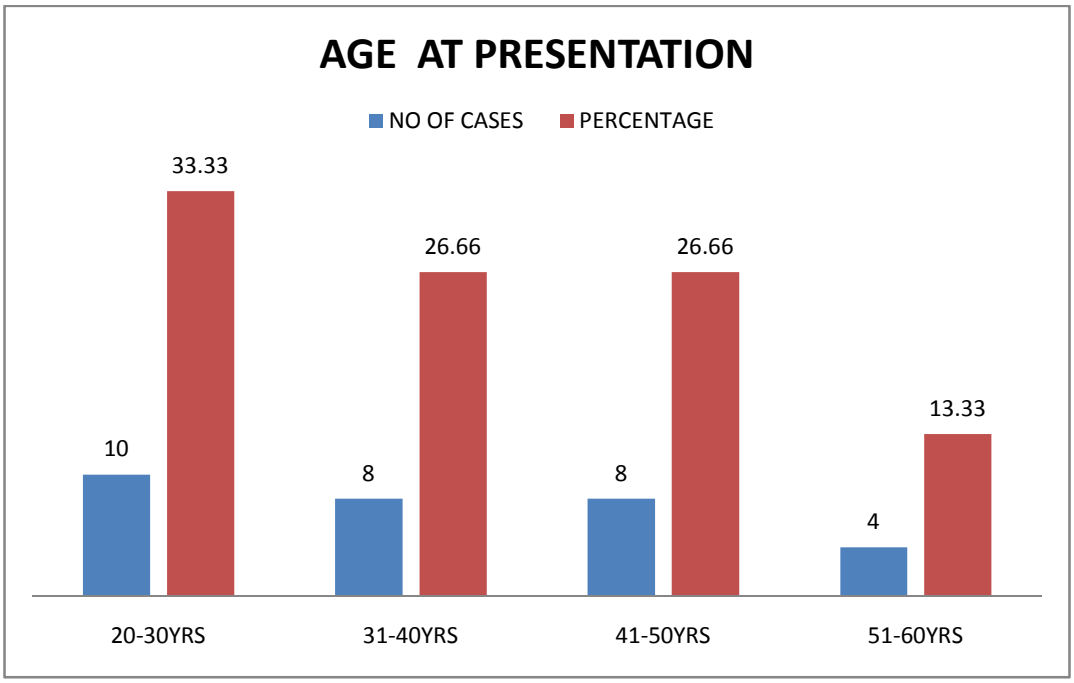
OBSERVATION AND DISCUSSION

In the present study, total number of 30patients in the age group of 20-60 years with clinical features of active Thyroid Eye Disease were examined for the following:

AGE GROUP AT PRESENTATION

Table -1

AGE	NO OF PATIENTS	PERCENTAGE
20-30YRS	10	33.33
31-40YRS	8	26.66
41-50YRS	8	26..66
51-60YRS	4	13.33

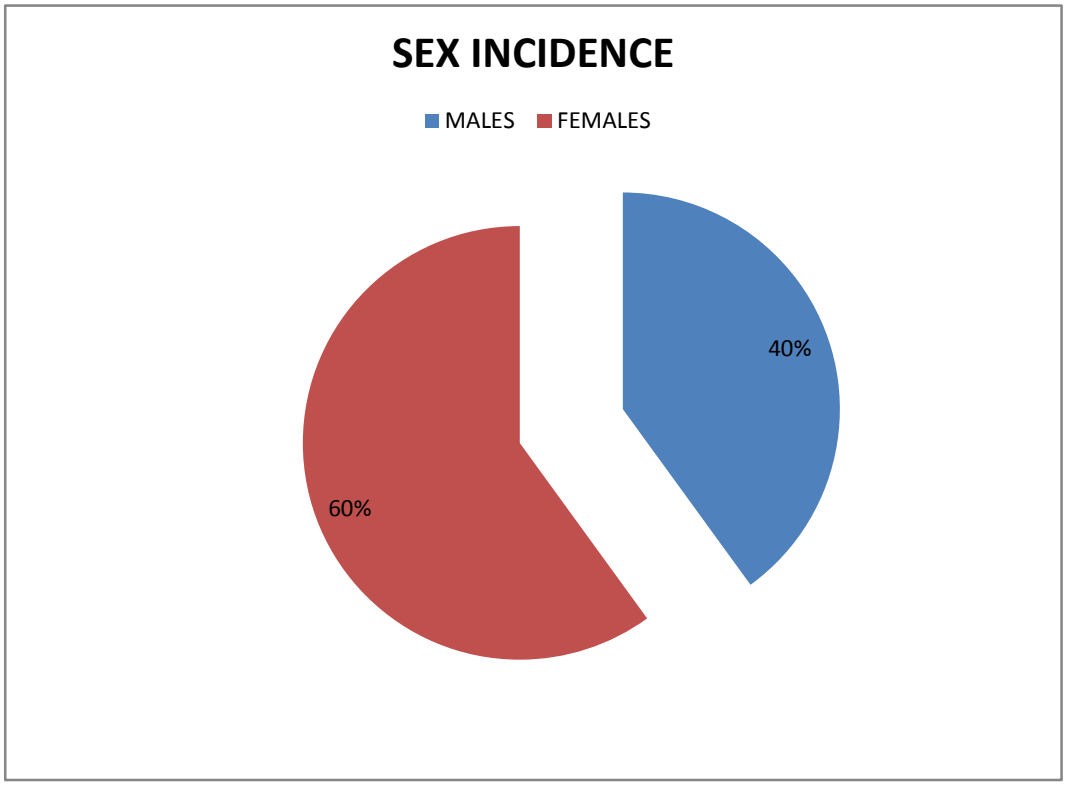


The mean age of presentation in our study is 38.86. Most common age group being 20-30 years (33.33%). Our study was compared with study by Bartelena et al which showed two peak incidence 5th and 7th decade[41.]

SEX DISTRIBUTION

Table 2

MALES	12(40%)
FEMALES	18(60%)

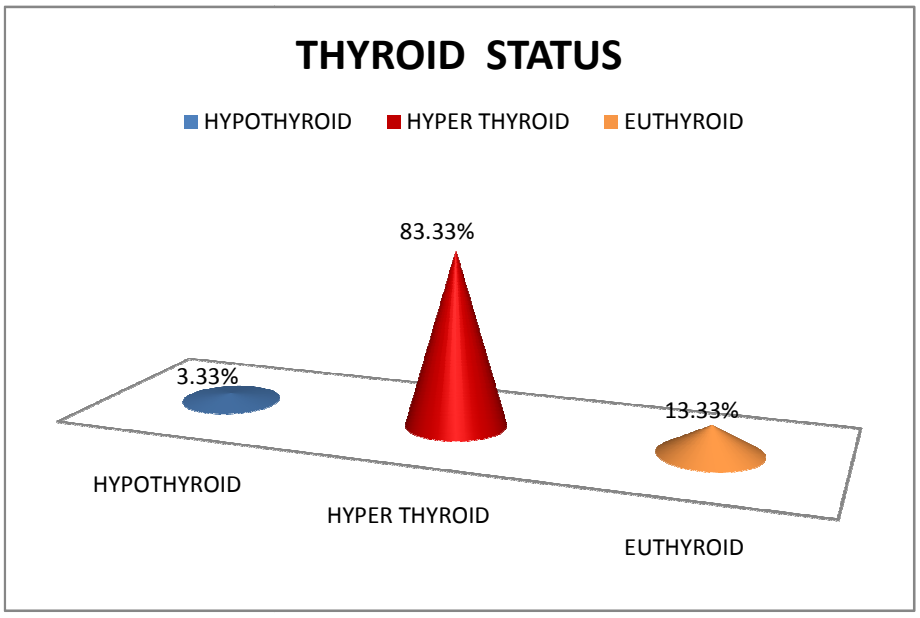


In our study there were 60% females and 40%males.The female: male ratio is 1.5 and the ratio is 0.5 in severe form of disease which was correlating to the study conducted by Prummel et al and Haage E et al[42]. Our study shows that males have severe form of disease in 66.66% as compared to females 33.33%, with the associated smoking as risk factor. It is compared with the study by Haage E et al[42.] which showed Cigarette smoking plays an important role in the occurrence of the ophthalmopathy and is also associated with a higher degree of disease severity and a lower effectiveness of its medical treatment.[42] Diabetes was present in 6.66% of patients in our study which was correlating with the study done by Prummel et al[40] which showed 10% association with TED and considered it to be an significant risk factor.

THYROID STATUS

Table 3

HYPOTHYROID	1(3.33)
HYPERTHYROID	25(83.33)
EUTHYROID	4(13.33)

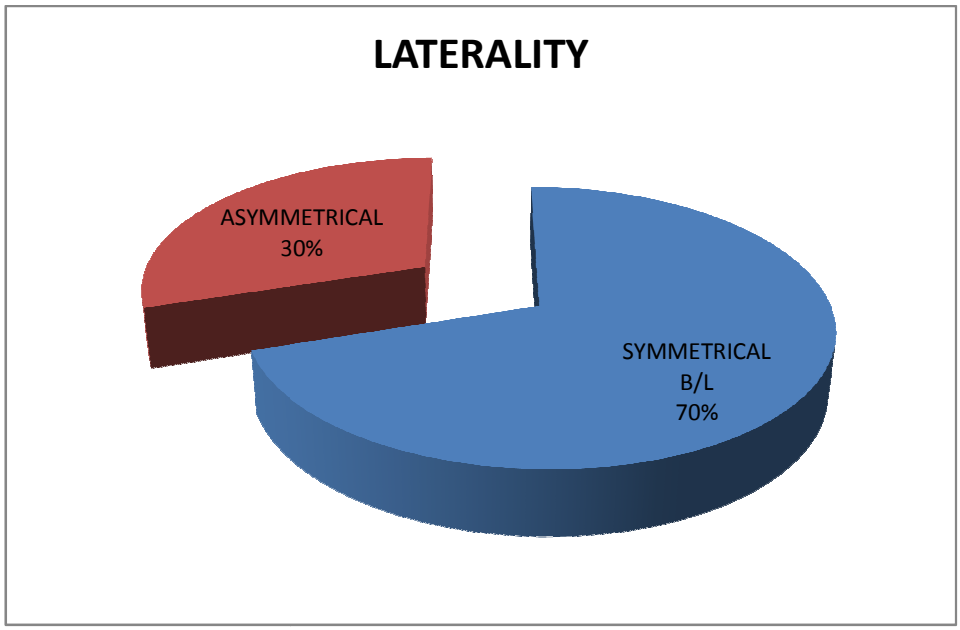


In our study the disease process was most common in 83.33% in Hyperthyroid patients, 3.33% in Hypothyroid patient and 13.33% in Euthyroid patients and these parameters were comparable with the study conducted by Prummel et al.[40]Another study conducted by Bartley et al showed that Graves ophthalmology was more frequent in Hyperthyroidism (90%),3% in Hypothyroidism and 6% in Euthyroid which was also correlating with our study.[44]

LATERALITY

Table 4

SYMMETRICAL B/L	ASYMMETRICAL B/L
21(70%)	9(30%)

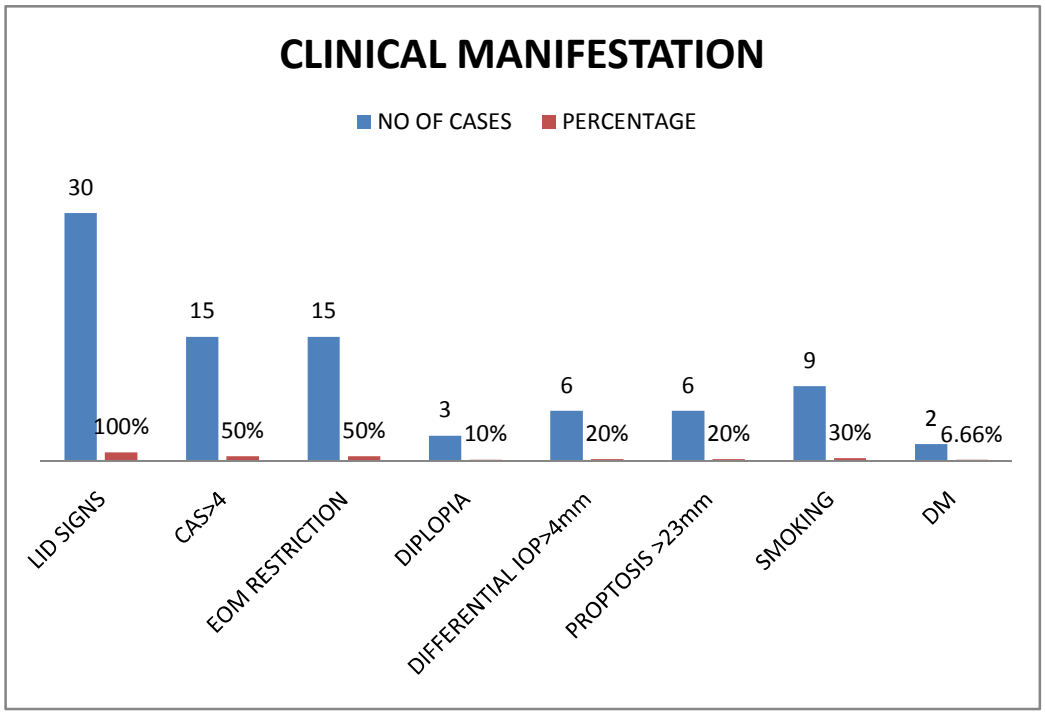


70% patients had bilateral and symmetrical involvement whereas 30% presented asymmetrically. The study was comparable with the study conducted by Bartley et al[13].

CLINICAL MANIFESTATION

Table 5

CLINICAL MANIFESTATION	NO OF PATIENTS	PERCENTAGE
LID SIGNS	30	100%
SOFT TISSUE INFLAMMATION WITH CAS >4	15	50%
OCULAR MOVEMENT RESTRICTION	15	50%
DIPLOPIA	3	10%
ACTIVE STAGE MILD MODERATE SEVERE	 15 9 6	 50% 30% 20%
OPTIC NERVE COMPRESSION	-	-
DIFFERENTIAL IOP >4mm	6	20%
PROPTOSIS >23mm	6	20%
IMAGING-CT ORBIT		
EOM ENLARGEMENT	12	40%
FAT HYPERTROPHY	3	10%
RISK FACTORS		
SMOKING	9	30%
DM	2	6.66%



In our study proptosis with lid retraction was most common initial presentation .Subjective symptoms like Oppressive Retro orbital feeling and pain on eye movement was present in all our patients. (mouritus et al1989,bartley et al1996b)[40].

Objective signs like Conjunctival congestion was present in 73.33% and eyelid swelling in 33.33%.Severe proptosis >23mm was present in 20%.Extraocular movement restriction was present in 50% but 10% presented with intermittent diplopia, the differential IOP elevation >4mm was found in 20% of these patients which is correlated with the study by

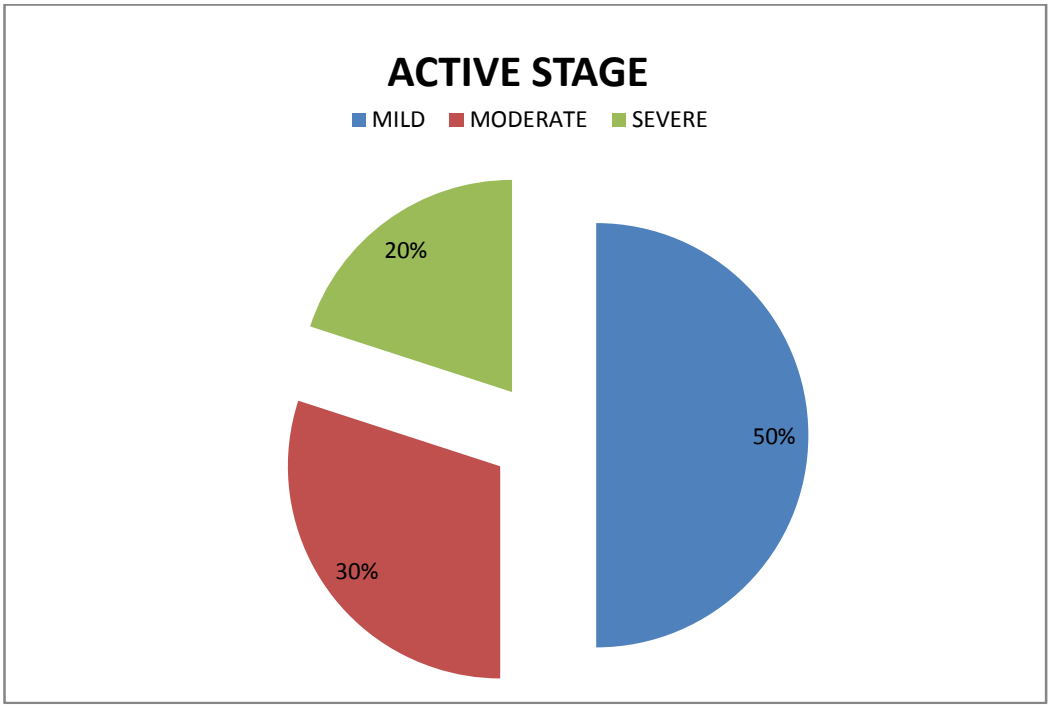
Bartley et al 1996b which states that 50% of orbitopathy presents with motility restriction .[13]

Soft tissue features were present in 50% of our patients which was compared to the study by kendler et al 1993 and Bartley et al 1996b[13], which showed association of soft tissue features in 34-75%.

In our study, 83.33% of patients presented with 6/6 Vision with correction, 6/18-6/12 in 13.33% which was due to cataractous changes and 3.33% with vision <1/60 which was due to associated Retinitis pigmentosa and cataract .No patient presented with vision loss due to optic nerve compression or corneal involvement in our study.

Patients were categorized as mild by insidious onset,lid lag,lid retraction,minimal proptosis,moderately active based on lid signs,soft tissue changes,moderate proptosis with intermittent myopathy,imaging showing disproportionate proptosis with mild extraocular enlargement.severe stage is characterized by rapid onset with predominant inflammatory and mass effects,progressive myopathy and compressive optic neuropathy, imaging showing evidence of extraocular muscle enlargement with apical crowding.

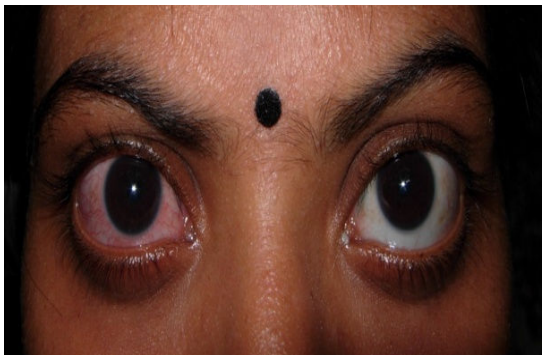
CLINICAL ACTIVITY



Patients presenting with clinical activity score >4 was categorized as mild stage in 50% of patients, moderately active in 30% and severe disease in 20% of patients. Our study was correlating with the study conducted by Bartley et al[13].

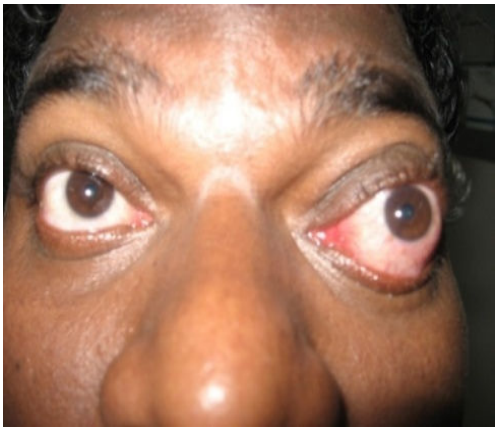
MILD STAGE

MODERATE ACTIVE STAGE



MODERATE INACTIVE STAGE

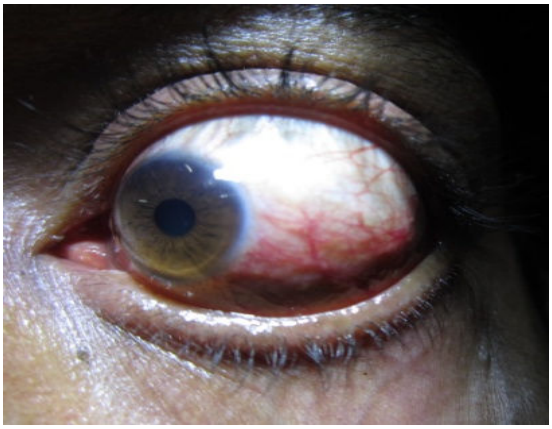
SEVERE ACTIVITY



LID EDEMA

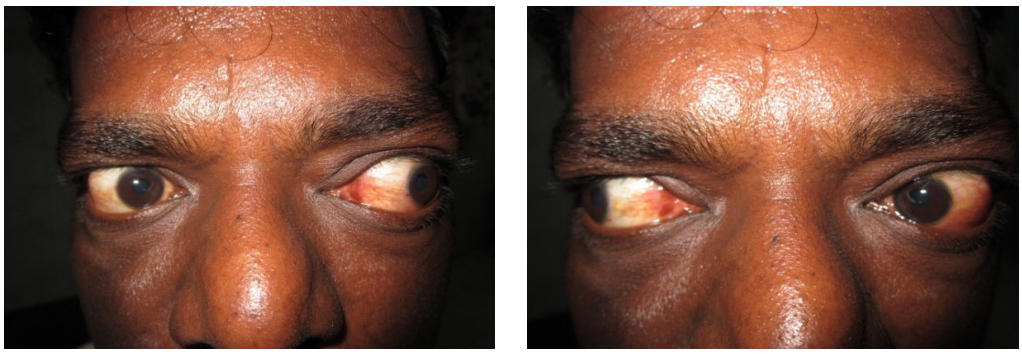
PERIOBITAL PUFFINESS

CONJUNCTIVAL CONGESTION



GOITER

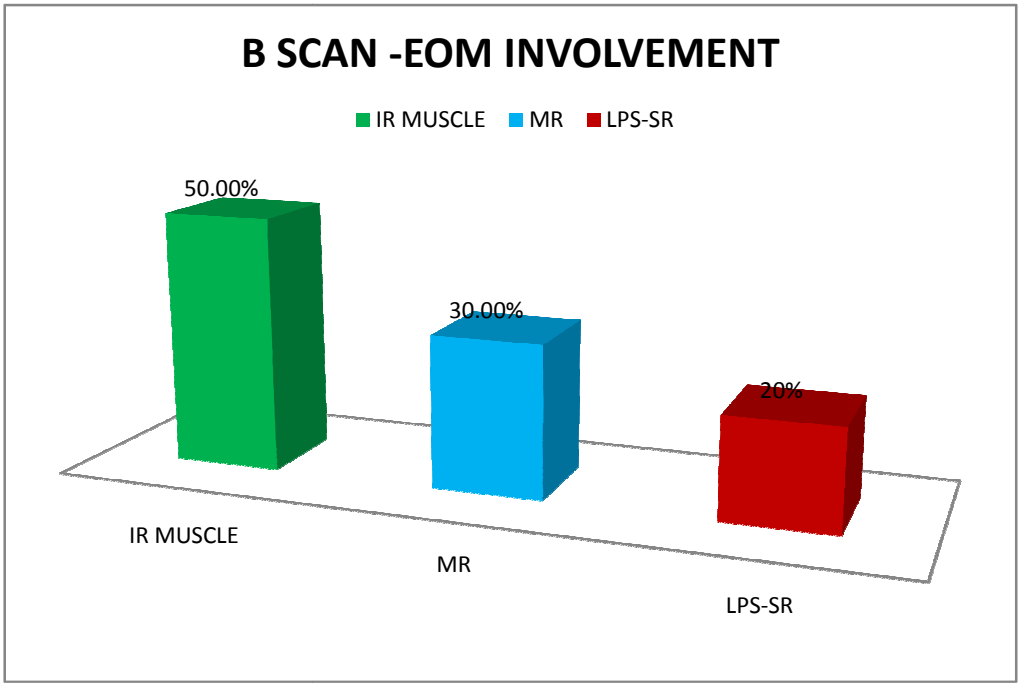
EXTRAOCULAR MOVEMENTS RESTRICTION



B SCAN

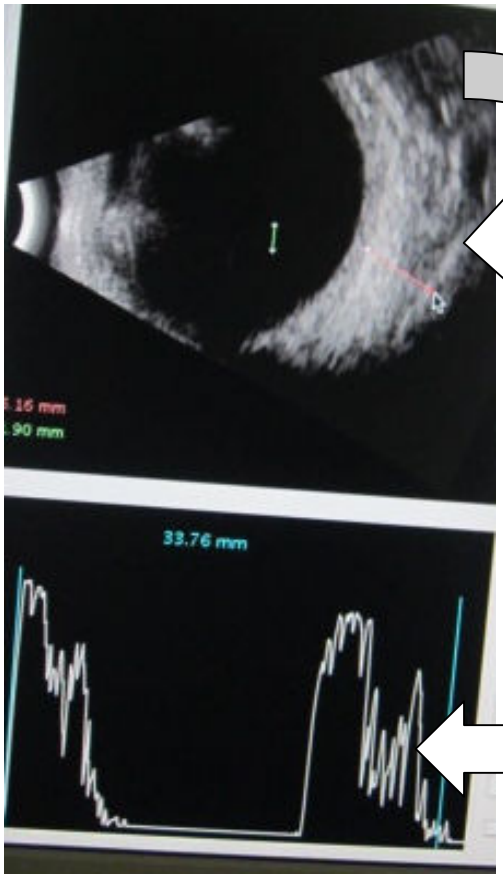
Table 6

EOM THICKENING	NO OF PATIENTS	PERCENTAGE
IR MUSCLE	15	50%
MR MUSCLE	9	30%
LPS-SR	6	20.00%



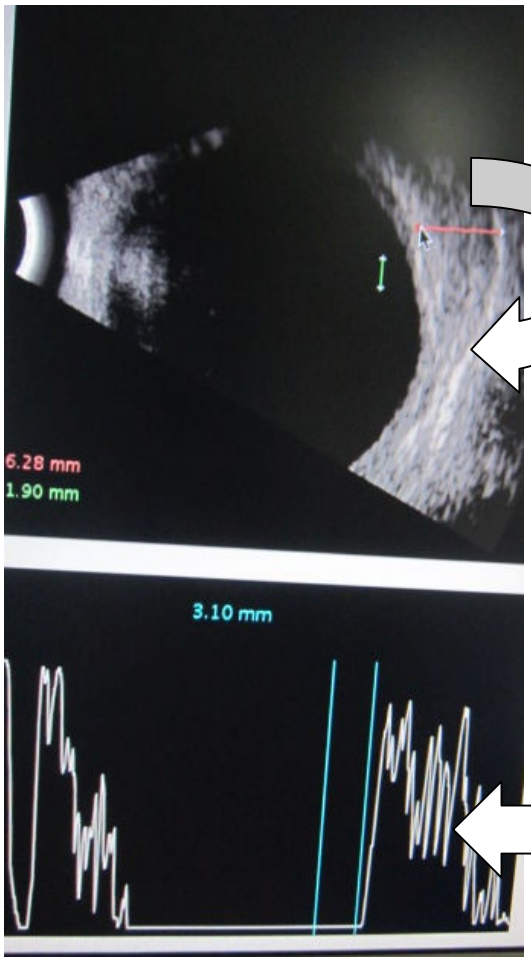
The B scan was done in longitudinal mode and the extraocular muscle thickness was compared with normative data given by Byrene et al. Inferior rectus was most frequently involved about 50% followed by medial rectus 30% and LPS-SR in 20% of our patients. Our study was comparable to the study by EVnagi et al which showed that the inferior rectus (93%) were the most frequently enlarged ,Medial, lateral and superior rectuses were enlarged in 59%, 37% and 34% of the orbits respectively.[37]

B SCAN



TENDON SPARING MR MUSCLE ENLARGEMENT

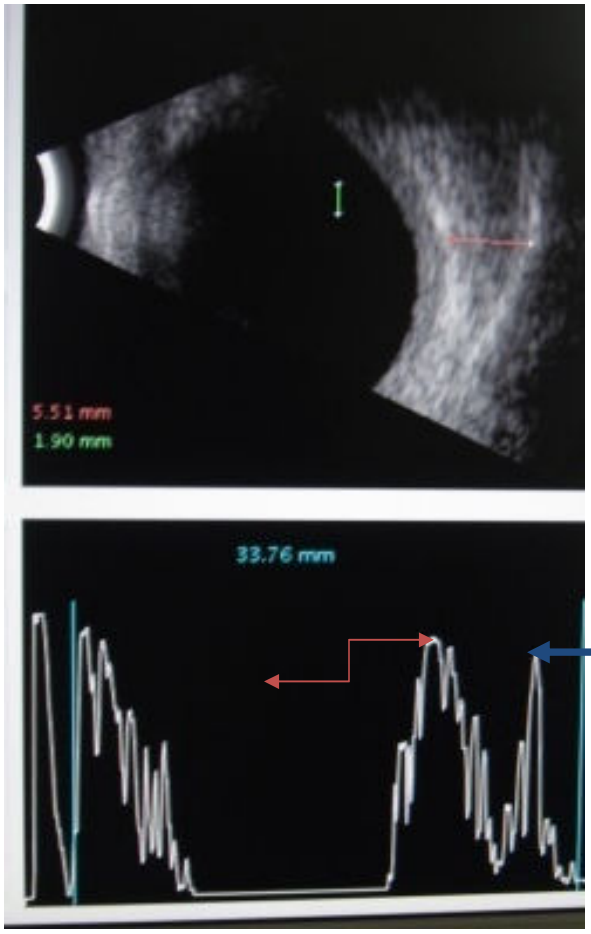
A SCAN SHOWING LOW MUSCLE REFLECTIVITY



TENDON SPARING MUSCLE ENLARGEMENT

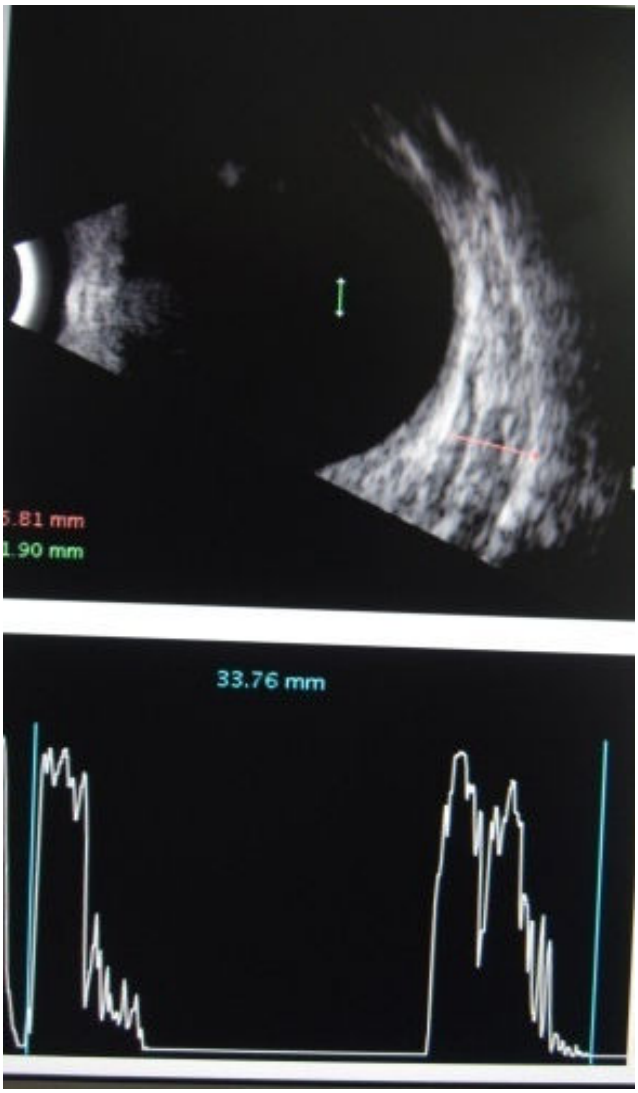
A SCAN SHOWING LOW EYE MUSCLE REFLECTIVITY

MEDIAL RECTUS

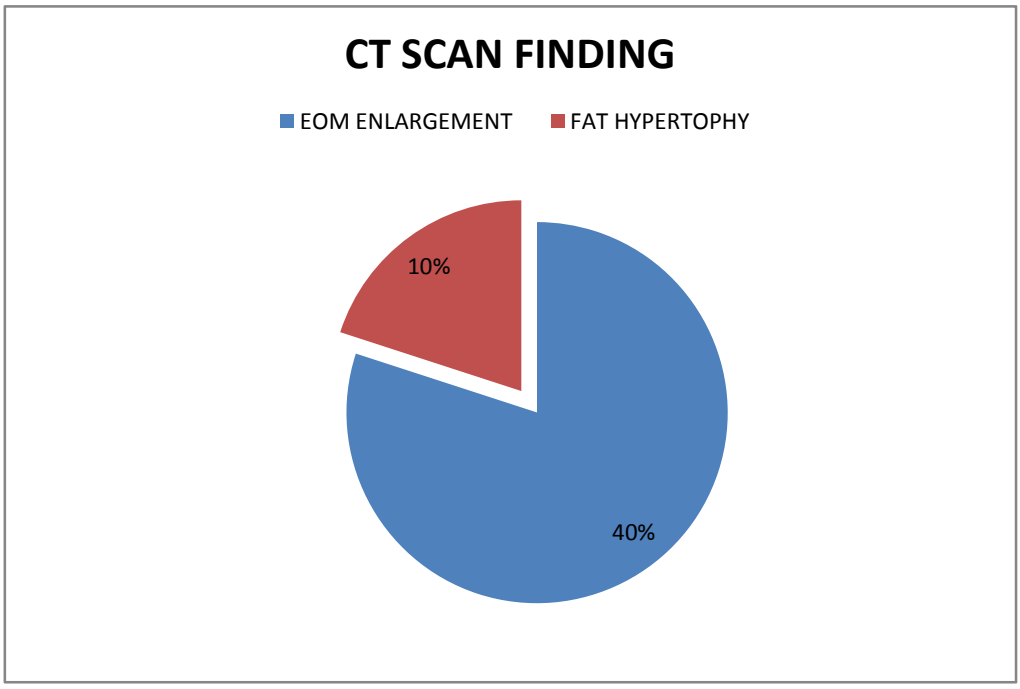


DOUBLE SPIKE
INDICATING MUSCLE

INFERIOR RECTUS

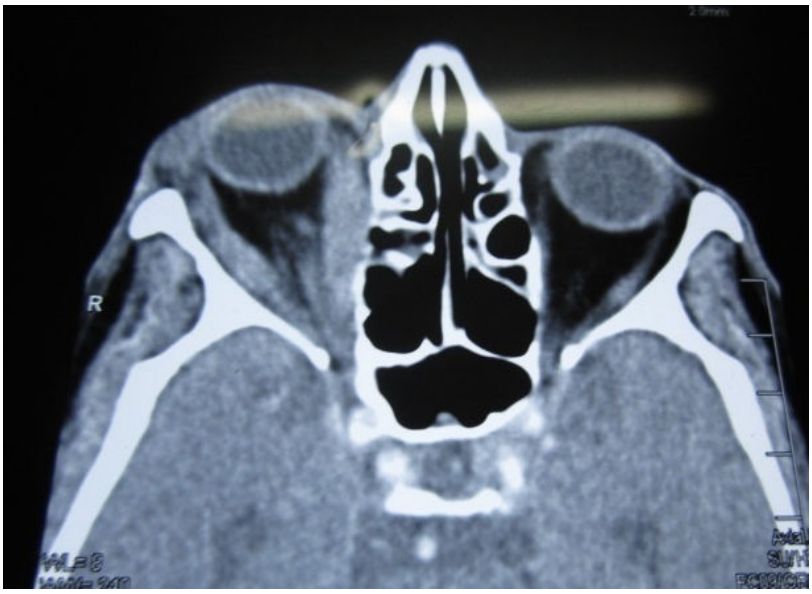


CT ORBIT AXIAL AND CORONAL VIEW

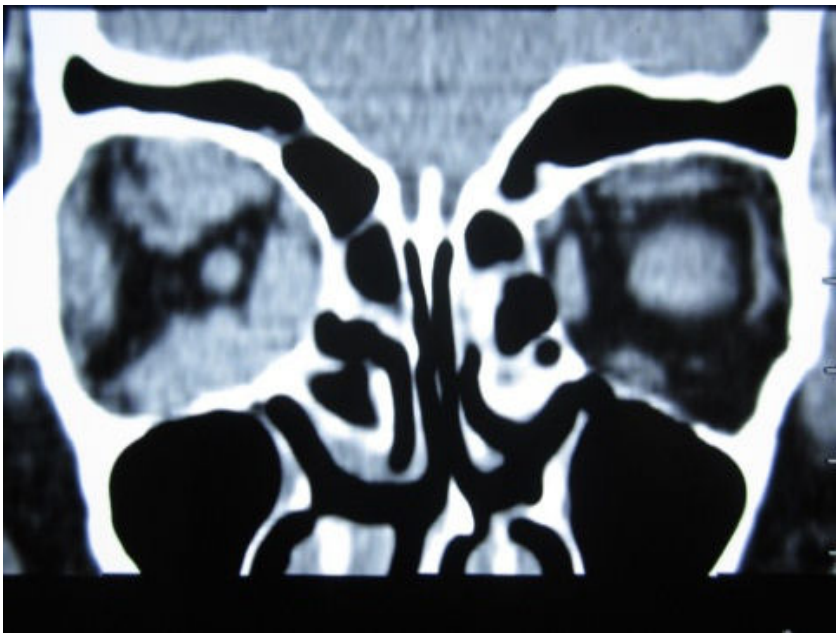


CT orbit was done for all the patients. Extraocular muscle enlargement was present in 40% patients and fat hypertrophy in 10% of patients. The fat hypertrophy was more frequent in young individual. Our study correlating with the study, Graves Orbitopathy - Current Imaging procedures by Berhard Krish et al.[26]

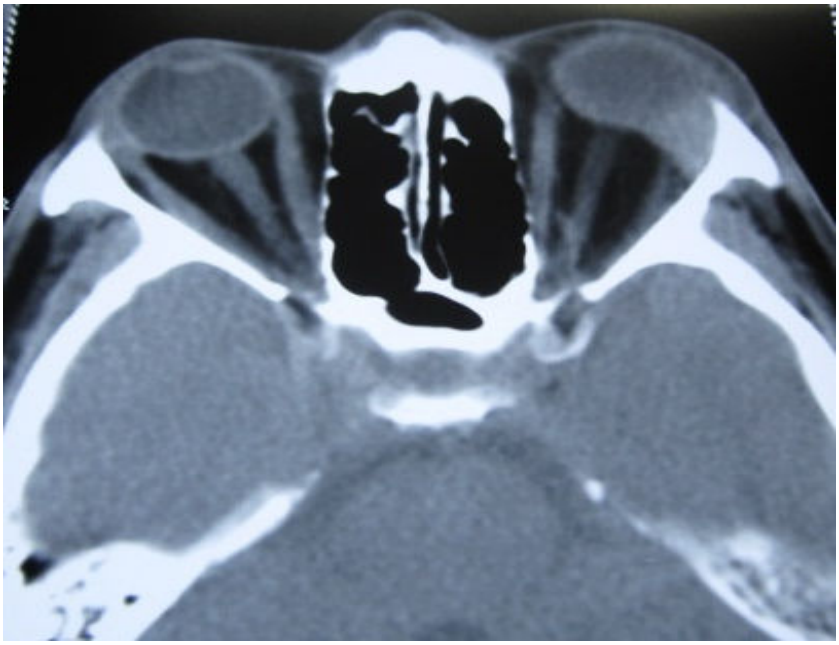
CT ORBIT AXIAL SCAN



CT CORONAL VIEW



FAT HYPERTROPHY



BIOCHEMICAL ANALYSIS

Biochemical investigation included TFT, IL-6, HS-CRP. The serum samples of patients in moderate and severe stage were taken and IL-6 and HS-CRP was done using ELISA technique and the results were compared with control group without TED.

The results were analyzed using ANOVA followed by TURKEY HSD test. The P value was significant at 5% level for both IL-6 and HS-CRP[30] in severely active patients and was not significant in moderate activity group. The mean difference was significant at 0.05 level when severe group was compared with control group and not significant when moderate group was compared with control group. There was no correlation between IL-6 and HS-CRP in the same group. Similar study conducted by Prummel et al states that proinflammatory cytokines like IL-1b, IL-6 and IL-10 are elevated in active TED when compared to inactive stage.[38] Another study by Molnar and Balazs found that significantly increased serum IL-6 was found in Graves Ophthalmopathy and suggested that IL-6 may be an important factor in the inflammatory events of Graves' opthalmopathy.[32]

ANOVA FOLLOWED BY TURKEY HSD TEST

IL-6

Activity	N	Mean	Standard deviation	P value
Severe	6	102.5317	150.58581	0.013*
Moderate	9	2.0311	.41093	
Control	18	15.4328	26.81282	
Total	33	27.6139	72.42253	

Note :* denotes significance at 5% level.

POST HOC TEST: TURKEY HSD

(I)group	(J)group	Mean difference	Standard error	P value
Severe	Moderate	100.5006(*)	34.10272	0.016*
	control	34.10272	30.50240	0.021*
Moderate	control	-13.4017	26.41586	0.868

*The mean difference is significant at 0.05 level.

HS-CRP

ANOVA

Activity	N	Mean	Standard deviation	P value
Severe	6	4.9233	4.69085	0.041*
Moderate	9	3.3444	3.22068	
Control	18	1.7722	.85530	
Total	33	2.7739	2.81818	

POST HOC TEST : TURKEY HSD

(I)group	(J)group	Mean difference	Standard error	P value
Severe	Moderate	1.5789	1.37921	0.495
	control	3.1511(*)	1.23360	0.041*
Moderate	control	-1.5722	1.06833	0.319

*The mean difference is significant at 0.05 level.

CORRELATIONS

Activity	Correlation between IL6 and HS - CRP	P Value
Severe	-0.399	0.433
Moderate	0.054	0.891
Control	0.150	0.553

Not significant

PITFALLS

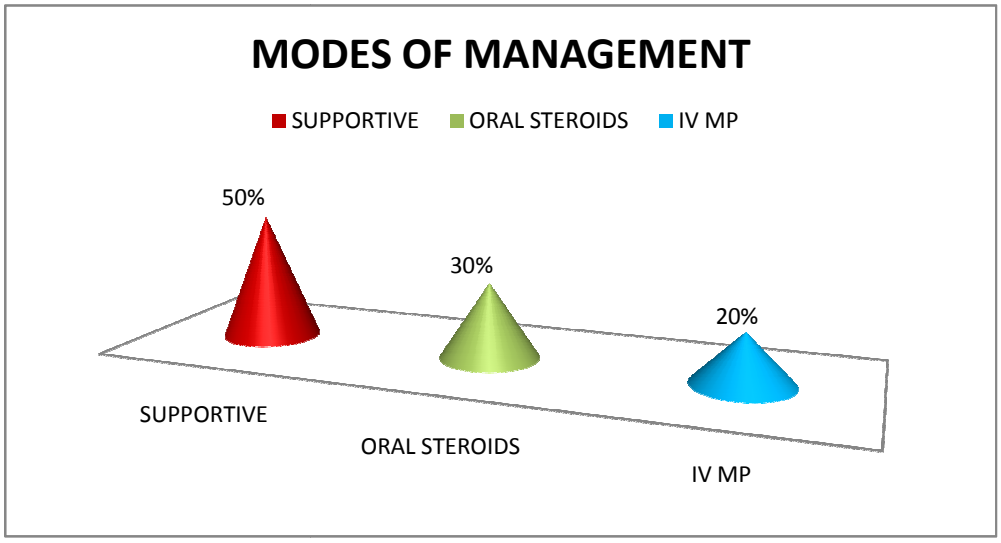
Though IL-6 and HS-CRP was statistically significant in severe disease, the role of these investigation in moderate disease could not be assessed because the sample size was small in our study.IL-6 is ELISA based analysis which is expensive and needs trained personnel to perform the procedure. So it could not be routinely used to screen the patients for activity of the disease.

HS-CRP is nonspecific inflammatory marker and again its role in moderately active stage could not be assessed in TED.

MANAGEMENT

Table 7

Mode of Treatment	No of Patients
Supportive therapy	15 patients (50%)
Oral steroids	9 patients (30%)
IV MP	6 patients (20%)

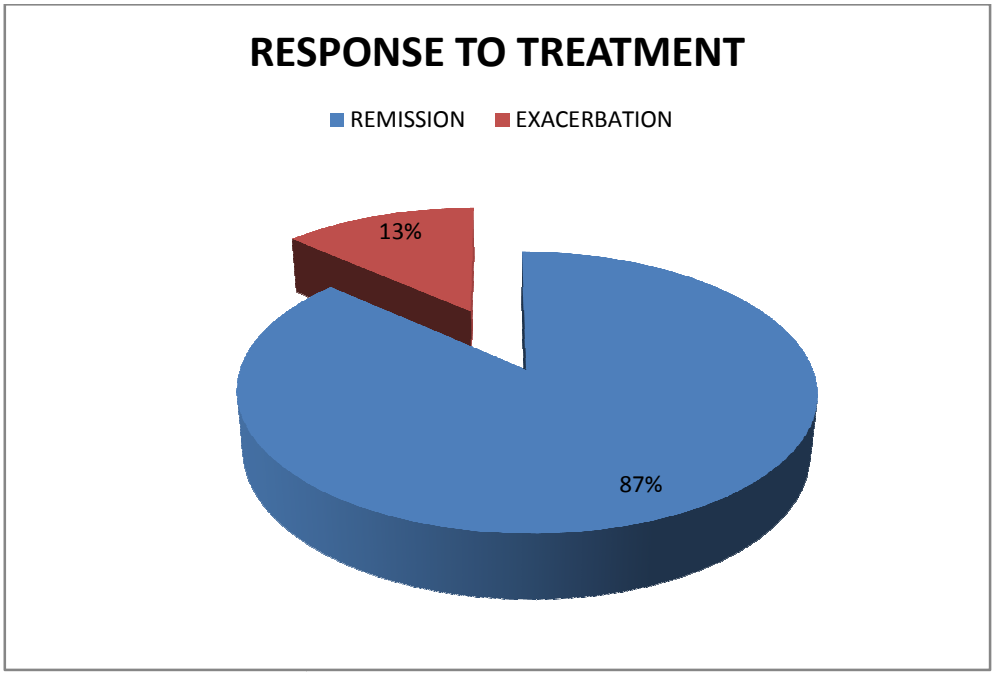


The patients in Mild stage (50%) were treated with supportive therapy like topical lubricants and head end elevation.30% of patients in moderately active stage were treated with oral steroids and 20% of them in severe stage with IV Methyl Prednisolone pulse therapy 1gram in 500ml of Normal saline for 3 days followed by oral steroids 40-60mg. Patients were followed weekly and assessed for disease activity for first 4 weeks.

FOLLOW UP

Table 8

Response to treatment	No of patients
Remission	26 (86.66%)
Exacerbation	4(13.33)



FOLLOW UP

The patients in mild stage who were treated with supportive management were followed up every 6 months, moderate and severely active patients who were put on either oral or intravenous steroid respectively were followed up weekly and biweekly respectively till 4 weeks to assess the response to treatment. Visualacuity, slit lamp examination, differential IOP, fields, colour vision, Hertels exophthalmometry, Blood Pressure recording, Random Blood glucose and systemic side effects of steroid therapy were monitored. Follow up showed remission in 86.66% patients in mild and moderately active stage where as 13.33% patients in severe stage treated with IV Methylprednisolone pulse therapy showed exacerbation after 6months.Those patients were treated with pulse therapy again, followed by oral steroids.Remission was attained in all our patients with steroid treatment. The study conducted by Thambe K Bargawa concluded that IV Methylprednisolone is more effective in moderate and severely active TED patients.[39]Eyelid retraction remained the same in all patients and were symptomatically better, inflammatory signs were reduced and disease progression was curtailed. The patients were then followed up monthly for 6 months and 3monthly thereafter for 1 year.

RESULTS

A total of 30 patients in the age group of 20-60years with thyroid eye disease were studied over the period of two years for age at presentation, sex incidence, presenting clinical features, thyroid status and disease activity, associated risk factors. All the patients underwent detailed clinical evaluation, supportive investigation was done and treatment was recorded.

1. Of the 30 cases examined, most common age group was between 20-30years (33.33%), females (60%) are most commonly affected than males.

2. The disease process was most common in Hyperthyroid(83.33%) patients as compared to Hypothyroid (3.33%) and Euthyroid status (13.33%).Risk factors associated with TED in our study was smoking in 30% and Diabetes Mellitus in 6.66%

3. 70% patients had bilateral and symmetrical involvement whereas 30% presented asymmetrically.

4. Proptosis with lid retraction was most common initial presentation.

5. Subjective symptoms like oppressive retro orbital feeling and pain on eye movement was present in all our patients.

6. Objective signs like Conjunctival congestion was present in 73.33% and Eyelid swelling in 33.33%.Severe proptosis >23mm was present in 20% and soft tissue features were present in 50% of our patients.

7. Extraocular movement restriction was found in 50% of patients in moderate and severely active patient, associated with diplopia only in 10% patients, and differential IOP of >4mm difference in about 20% 0f them.

8. Visual acuity with Snellen chart showed 6/6 in 83.33%, 13.33% patients had 6/18-6/12 due to cataractous changes, 3.33% patients with vision <1/60 which was due to associated Retinitis Pigmentosa and cataract.

9. Patients presenting with clinical activity score >4 were categorized as moderately active in 30%, severe disease in 20%, mild stage in 50% of patients.

10. CT ORBIT axial and coronal view showed tendon sparing muscle enlargement in 40% of patients and fat hypertrophy in 10% of patients. Fat hypertrophy was more common in younger patient.

11. B SCAN- Tendon sparing EOM thickening was found in longitudinal mode and the maximum muscle belly was measured, corresponding low eye muscle reflectivity was noted in A scan. Inferior rectus was most frequently involved (50%) followed by medial rectus (30%) and LPS –SR complex in (20%).

12. The patients in moderate and severely active stage, IL-6 and HS-CRP was done which was compared with control group without TED and the results were analyzed using ANOVA followed by TURKEY HSD test. The P value was significant at 5% level for both IL-6(0.013) and HS-CRP(0.041) in severely active patients and was not significant in moderate activity group. The mean difference was significant at 0.05 level with the P value of .016 when severe group was compared with moderate and control group and not significant when moderate group was compared with control group.

13. 50% of the patients presented as mild disease who were treated with supportive therapy. Moderatly active patients (30%) were treated with oral steroids and 20% of the patients in severely active phase were treated with pulse Intravenous Methylprednisolone followed by oral steroids.

14. Follow up showed remission in 86.66% patients in mild and moderately active stage where as 4 patients in severe stage treated with iv methylprednisolone pulse therapy showed exacerbation after 6months.Those patients were treated with pulse therapy again, followed by oral steroids. Remission was attained in all our patients with steroid treatment, Eyelid retraction remained the same in all patients.

CONCLUSION

1. Clinical assessment remains the paramount importance in diagnosing the activity in Thyroid Eye Disease although controversies do exist in clinical evaluation and management.

2. A scan with orbital B scan aids in the diagnosis of thyroid eye disease in active stage, which is very economical with relatively short examination time and no risk of radiation .Follow up of the patients can also be performed easily.

3. IL-6 and HS-CRP was statistically significant at 5% in patients with severe disease when compared to control group. The correlation in between HS-CRP and IL-6 in all three groups were not significant. Though the parameters shows significance for severe disease, its role in moderate disease could not be assessed.

4. Identifying the disease activity early and aggressive management with systemic steroids in moderately active and severe stage has decreased the morbidity associated with the disease.

PART- III

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PROFORMA

Name:

Age: **Sex:** **IP No:** **DOA**: **DOD:**

Address:

Complaints: Onset, duration, rate of progression

Pain

Redness and edema of lids and conjunctiva

Photophobia

Diplopia

Forward protrusion of eyes

Defective vision

Past history:

Duration of thyroid dysfunction:

Symptoms pertaining to thyroid disorder:

Hypothyroidism--Weight gain/ Cold intolerance/ Fatigue/ constipation/ mennorrhagia/ poor memory/ depression

Hyperthyroidism—weight loss inspite of increased apetite /heat intolerance/ restlessness/ diarrhea/ amnorrhoea/ irritability/ tremors and palpitation Presence of swelling in the neck.

Treatment history:

Personal history: Smoking / diabetic/ Hypertention

General Examination:	Nutrition	Pallor
	Cyanosis	Clubbing
	Tremors	Icterus

Pulse rate **Blood Pressure:**

C.V.S

R.S

C.N.S

Thyroid examination:

Ocular examination

Head posture Facial symmetry

RE **LE**

Lid

Lid signs

Position

Redness

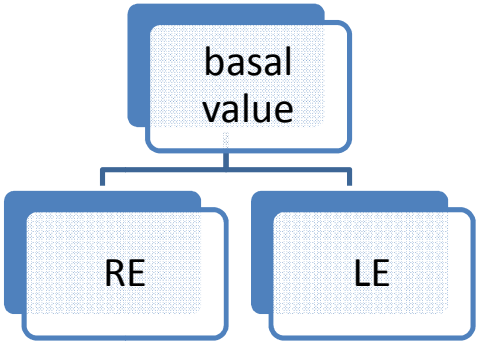
Swelling

lagophthalmos

Orbit

Proptosis-axial/eccentric

Hertels Exophthalmometry



Pulsation

Compressibility/reducibility

Mass/resistance to retropulsion

Valsalva's maneuver

Visual acuity by snellens chart

Slit lamp examination of anterior segment

Extraocular movements

Conjunctiva-congestion/chemosis/cauncle edema

Cornea –Exposure keratitis

Stain,sensation,schirmers test

Anterior chamber

Pupil

Lens

Fundus examination

Colour vision **Fields**

Differential IOP

Diplopia charting **FDT**

Investigation

Complete haemogram,R.B.S,Thyroid function test,IL-6,HS-CRP

B scan with A scan,CT orbit –Axial and Coronal view.

Treatment

Endocrinologist opinion

Supportive management with topical lubricants

Oral steroids/I.V pulse therapy with methylprednisolone

FOLLOWUP:

KEY TO MASTER CHART

T.STA-Thyroid status

GEN-General Association

Vn-Visual acuity

CAS-Clinical Activity Score

EOM-Extraocular Movement Restriction

DI ACT-Disease activity

LS-Lid Signs

DIP-Diplopia

D IOP-Differential IOP >4mm

A/BS-A Scan/B Scan

CT-CT scan

IL-IL-6

HS-HS-CRP

MAN-Management

FOL UP-Follow up

MASTER CHART

S. No.	Name	AGE	SEX	T.STA	GEN	Vn	CAS	EOM	DI ACT	LS	DIP	D IOP	A / B S	CT	IL	HS	MAN	FOL UP
1	ELLAPPAN	57	M	HYP	S+,DM+	6/24 PH 6/6	4	PRE	SEV	PRE	PRE	PRE	Lref	E enl	1.8	0.9	IVMP	EXA
2	MURALI	30	M	EU	NS	6/6BE	2	ABS	MIL	PRE	ABS	ABS	NR	Enor			Sup	Rem
3	BALAJI	29	M	EU	S+,DM+	6/6BE	5	PRE	SEV	PRE	PRE	PRE	Lref	E enl	50	11	IVMP	Rem
4	MANJULA	30	F	HYP	G+	6/6BE	2	ABS	MIL	PRE	ABS	ABS	NR	Enor			Sup	Rem
5	RAJENRAN	50	M	HYP	S+,DM+	6/12 PH 6/9 BE	2	ABS	MIL	PRE	PRE	ABS	NR	Eenl			Sup	Rem
6	NASEERABANU	43	F	HYPO	NS	6/24PH 6/12BE	4	PRE	MOD	PRE	ABS	ABS	Lref	Eenl	1.9	3.3	OS	Rem
7	SUBBULAKSHMI	25	F	HYP	G+	RE-6/6,LE-6/9PH 6/6	2	ABS	MIL	PRE	ABS	ABS	NR	Enor			Sup	Rem
8	PRABHA	32	F	HYP	NS	BE 6/9PH 6/6	4	PRE	MOD	PRE	ABS	ABS	Lref	Eenl	1.8	11	OS	Rem
9	KAMALA	25	F	HYP	G+	6/6BE	2	ABS	MIL	PRE	ABS	ABS	NR	Enor			Sup	Rem
10	JAYANTHI	43	F	HYP	G+	6/6BE	4	PRE	MOD	PRE	ABS	ABS	Lref	Eenl	2	3.7	OS	Rem
11	SABARI	28	F	HYP	G+	6/6BE	2	ABS	MIL	PRE	ABS	ABS	NR	Enor			Sup	Rem
12	AMMUKUTTI	24	F	HYP	G+	6/6BE	4	PRE	MOD	PRE	ABS	ABS	Lref	Eenl	1.8	0.2	OS	Rem
13	AMMU	35	F	HYP	G+	6/6BE	2	ABS	MIL	PRE	ABS	ABS	NR	Enor			Sup	Rem
14	SUSHEELA	45	F	EU	RP	HM	4	PRE	SEV	PRE	ABS	PRE	Lref	Eenl	2.2	1.3	IVMP	Exa
15	VADIVEL	32	m	HYP	s+	6/6BE	2	ABS	MIL	PRE	ABS	ABS	NR	Enor			Sup	Rem
16	RAJAN	52	M	HYP	S+	6/6BE	4	PRE	MOD	PRE	ABS	ABS	Lref	Eenl	1.4	1.1	OS	Rem
17	YAMUNA	54	F	HYP	NS	6/6BE	2	ABS	MIL	PRE	ABS	ABS	NR	Enor			Sup	Rem

S. No.	Name	AGE	SEX	T.STA	GEN	Vn	CAS	EOM	DI ACT	LS	DIP	D IOP	A / B S	CT	IL	HS	MAN	FOL UP
18	NITHYA	25	F	HYP	NS	6/6BE	2	ABS	MIL	PRE	ABS	ABS	NR	Enor			Sup	Rem
19	KADHAR MEERA SAHIB	46	M	EU	S+	BE 6/9PH 6/6	4	PRE	SEV	PRE	ABS	PRE	Lref	Eenl	185	2.6	IVMP	Exa
20	KANAGARAJ	33	M	HYP	S+	BE 6/9PH 6/6	4	PRE	SEV	PRE	ABS	PRE	NR	FH	374	1.5	IVMP	Exa
21	MURALIDHARAN	43	M	HYP	S+	BE 6/6	4	PRE	MOD	PRE	ABS	ABS	Lref	FH	1.9	0.7	OS	Rem
22	VANITHA	29	F	HYP	G+	BE 6/6	2	ABS	MIL	PRE	ABS	ABS	NR	Enor			Sup	Rem
23	RAMESH	38	M	HYP	S+	BE 6/6	2	ABS	MIL	PRE	ABS	ABS	NR	Enor			Sup	Rem
24	VIJAYALAKSHMI	37	F	HYP	NS	BE 6/6	4	PRE	MOD	PRE	ABS	ABS	Lref	Eenl	2.3	5	OS	Rem
25	NEELAVATHI	43	F	HYP	NS	BE 6/9PH 6/6	2	ABS	MIL	PRE	ABS	ABS	NR	Enor			Sup	Rem
26	PUNITHA	36	F	HYP	G+	BE 6/24 PH 6/6	4	PRE	MOD	PRE	ABS	ABS	Lref	Eenl	2.8	2.6	OS	Rem
27	KILIAMMAL	60	F	HYP	NS	BE 6/36 PH 6/18	5	PRE	SEV	PRE	ABS	PRE	Lref	Eenl	2.6	2.2	IVMP	Rem
28	VASIM BISHAH	40	M	HYP	NS	BE 6/6	2	ABS	MIL	PRE	ABS	ABS	NR	Enor			Sup	Rem
29	MOHANKUMAR	28	M	HYP	NS	BE 6/6	4	PRE	MOD	PRE	ABS	ABS	Lref	FH	2.3	2.6	OS	Rem
30	RUKMANI	45	F	HYP	G+	BE 6/36 PH 6/18	2	ABS	MIL	PRE	ABS	ABS	NR	Eenl			Sup	Rem